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Beta cell function as an assessment tool for cardiovascular risk in patients with metabolic syndrome

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Abstract

Background/Aim: Epicardial fat tissue (EFT) is considered a cardiovascular risk factor independent from visceral adiposity, obesity, hypertension, and diabetes. Fasting serum C-peptide is a known marker of endogenous insulin secretion and beta cell function. Our aim was to evaluate C- peptide levels in patients with metabolic syndrome (MetS) in relation to the EFT thickness.
Methods: Forty-five subjects with MetS without a history of coronary artery disease and 25 healthy volunteers were enrolled this prospective case-control study. We examined the laboratory values, including C peptide, insulin, and HOMA-IR after 8 hours of fasting. EFT thickness was measured by two-dimensional transthoracic echocardiography.
Results: The serum C peptide levels were significantly higher in patients with metabolic syndrome compared to the healthy controls [3.41(1.98) ng/ml vs 2.07 (1.39), $P<0.001$]. C peptide levels were correlated with BMI ($P=0.032$, r=0.281) and serum triglycerides ($P=0.023$, r=0.288). Patients with MetS had remarkably high EFT thickness [0.63(0.22) mm, $P=0.043$]. EFT thickness was correlated with age ($P=0.008$, r=0.397), weight ($P=0.042$, r=0.308) and C-peptide ($P=0.002$, r=0.460) in patients with MetS.
Conclusion: EFT thickness and elevated C-peptide are independent risk factors influencing atherosclerosis. The strong association between EFT thickness and C-peptide demonstrated herein indicates that EFT may play an important role in C peptide secretion, possibly contributing to the cardiometabolic risk in patients with MetS.

Keywords: Metabolic syndrome, C-peptide, Epicardial fat tissue, Cardiovascular risk

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Introduction

Over the last ten years, the metabolic health of individuals worsened due to sedentary lifestyle and change in nutritional habits. In developed and developing countries, regardless of age, over-feeding related health problems have become a pandemic [1]. This has resulted in an increased incidence of metabolic syndrome (MetS) related diseases such as diabetes, obesity, hyperlipidemia, hypertension, which all lead to cardiovascular diseases [2].

Evidence shows that insulin resistance, inflammation and endothelial dysfunction are the ethologic mechanisms of metabolic syndrome. We all know that several indexes and biological markers were investigated to predict the cardiovascular risk scale of metabolic syndrome and related conditions [3]. Early detection of risk factors allows us to assess personalized treatment strategies in metabolic syndrome.

C-peptide originates from the middle part of proinsulin and is not only a valid marker for beta cell function but also suggested for use as an indicator for cardiovascular risk in patients with metabolic syndrome. Although the role of C-peptide in triggering vascular complications is still unclear, numerous studies hypothesize that it might contribute to plaque development in patients with insulin resistance and type 2 diabetes [4].

Epicardial fat tissue (EFT) is the visceral fat lateral to the right ventricle and the anterior wall of the left ventricle, which shares the same microcirculation with the myocardium. Recently, EFT was shown to perform a high rate of white adipose tissue lipolysis and lipogenesis which makes it a metabolically active organ. EFT is a triglyceride storage and suggested to release high levels of free fatty acid into the near myocardium and microcirculation in case of metabolic stress [5]. Previous studies suggested that echocardiographic EFT thickness measurement can be an indirect way to demonstrate atherosclerosis and left ventricular diastolic dysfunction as well as predict high cardio-metabolic risk and should be a therapeutic target [6].

This study aimed to evaluate C-peptide level in terms of EFT thickness in a representative sample of patients with metabolic syndrome and further demonstrate the C-peptide level of patients with high cardiovascular disease risk.

Materials and methods

Subjects and settings

Forty-five subjects with MetS were selected at an internal medicine outpatient policlinic. Criteria used for the diagnosis of metabolic syndrome were the recommendations of the National Cholesterol Education Program, Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults -Adult Treatment Panel III (NCEP-ATP III). Metabolic syndrome was defined by the presence of at least three of these components: *1*) Increased waist circumference (>102 cm for men, >88 cm for women) *2*) Elevated triglycerides (≥150 mg/dL) or the use of triglyceride-lowering drugs *3*) Low HDL-cholesterol (<40 mg/dL in men, <50 mg/dL in women), *4*) Hypertension (≥130 / ≥85 mmHg) or use of antihypertensive drugs, and *5*) Fasting glucose (≥110 mg/dL) or the use of antidiabetic drugs [7]. Exclusion criteria were the presence of cardiovascular disease, congenital heart disease, heart valve disease, neoplastic, inflammatory, and infectious diseases.

Physical and laboratory measurements

The collection of anthropometric data (weight, height, waist circumference) and measurement of systemic blood pressure were obtained by physical examination according to standard procedures. The BMI (body mass index) was calculated by dividing weight (kg) by height (m^2). Waist circumferences were measured in the horizontal plane midway between the lowest rib and iliac crest. Resting systolic and diastolic BP was measured using a standard mercury sphygmomanometer after a 5-min rest. Fasting venous blood samples were collected in the morning after at least 8 hours of fasting. Serum cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) were measured by enzymatic colorimetric methods with commercially available kits (COBAS 311, Roche Diagnostics GmbH, Mannheim, Germany), and low-density lipoprotein cholesterol C (LDL-C) was calculated according to the Friedewald formula. Serum glucose measures were determined enzymatically using the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany). HbA1c was determined with a COBAS 311 analyzer using the particle-enhanced immunoturbidimetric method (Roche Diagnostics, Mannheim, Germany). Final results were expressed as percent HbA1c of the total Hb according to the protocol of the Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program (DCCT/NGSP). The particle-enhanced immunoturbidimetric method with a Behring Nephelometer BN-100 (Behring Diagnostic, Frankfurt, Germany) was used to measure C reactive protein (CRP). The sensitivity of the test was 0.1 mg/L. C-peptide levels were determined by electrochemiluminescence (ECLA) assay in a random-access analyzer (Cobas E411, Roche Diagnostics, Les Pennes-Mirabeau, Bouches-du-Rhône, France). The homeostasis model assessment of insulin resistance (HOMA-IR) score was calculated using the formula defined by Matthews et al. (1985): HOMA IR = [fasting insulin (mU/mL) × fasting glucose (mmol/L)]/22.5 [8].

Measurement of echocardiographic epicardial fat tissue

Two-dimensional transthoracic echocardiography was performed by a single cardiologist. EFT thickness was performed using the DICOM system. The free wall of the right ventricle was measured from the papillary muscle at end-diastole from the parasternal long-axis views of three cardiac cycles, using the aorta annulus for anatomic reference. The thickest point of EFT was measured, and the mean value of the EFT thickness was calculated.

Statistical analysis

Statistical analysis was performed with MedCalc Statistical Software version 12.7.7 (MedCalc Software, Ostend, Belgium; http://www.medcalc.org; 2013). Values were expressed as mean (standard deviation) or as percentages. The student t-test was used for the comparison of two independent and normally distributed variables. The Mann Whitney U test was performed for the comparison of independent and non-normally distributed variables. The chi-square test and Fisher Exact test were

performed to determine the differences between categorical variables. Correlations of variables were assessed with Pearson's and Spearman analysis. Statistical significance was assessed at *P*-value <0.05.

Ethics approval

Our study was approved by Ethics Committee of GOP Taksim Education and Research Hospital with the decision number 103 on 05.08.2020 and conducted per the Declaration of Helsinki. Informed consent forms were signed by each participant.

Results

The study group consisted of 45 patients (30 females, 15 males) and 25 (14 females, 11 males) healthy volunteers. The patient group included metabolic syndrome patients without a cardiovascular disease history, with a mean age of 55.7 (11.43) years. When parameters obtained from those with metabolic syndrome and healthy volunteers are compared, patients with MetS were higher values in terms of systolic blood pressure, weight, waist circumference, BMI, fasting glucose, HbA1c, insulin, HOMA, triglyceride, ALT, GGT, CRP (*P*<0.001 for all). Serum fasting C-peptide levels were higher in the group with metabolic syndrome compared to the healthy group [3.41 (1.9) vs 2.07 (1.39), *P*<0.001]. The patients with metabolic syndrome had higher EFT thicknesses [0.63(0.22)] than the healthy group [0.52 (0.11)], (*P*<0.001) (Table 1).

Table 1: Clinical and biochemical characteristics of patients in the study

	Control (n=25) Mean(SD)	Metabolic syndrome (n=45) Mean (SD)	*P*-value
Age (years)	46.69 (8.1)	55.7 (11.43)	<0.001**
Gender			
Male	11(44%)	15(33.3%)	
Female	14(56%)	30(66.6%)	
SBP (mmHg)	119.23 (9.87)	134.89 (21.58)	<0.001**
DBP (mmHg)	70.96 (8.13)	75.34 (12.96)	0.176
WC (cm)	86.19 (11.31)	111.9 (13.36)	<0.001**
BMI (kg/m2)	25.77 (3.38)	34.02 (6.92)	<0.001**
Fasting glucose (mg/dl)	90.96 (11.12)	168.89 (93.2)	<0.001**
Hba1c (%)	5.52 (0.44)	8.18 (2.74)	<0.001**
Insulin (IU/ml)	7.46 (5.47)	28.22 (49.8)	<0.001**
C peptide (ng/ml)	2.07 (1.39)	3.41 (1.98)	<0.001**
HOMA-IR	1.62 (1.25)	3.41 (1.98)	<0.001**
TCH (mg/dl)	206.77 (38.36)	219.11 (46.74)	0.213
TG (mg/dl)	112.92 (54.9)	222.57 (167.99)	<0.001**
LDL-c (mg/dl)	130.19 (32.23)	130.7 (37.08)	0.953
HDL-c (mg/dl)	53.96 (13.94)	47.2 (9.3)	0.114
CRP (mg/dl)	2.46 (2.22)	5.75 (3.57)	<0.001**
EFT thickness (mm)	0.52 (0.11)	0.63 (0.22)	0.043*

BMI: body mass index, WC: waist circumference, TCH: total cholesterol, TG: triglycerides, HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, CRP: C reactive protein, EFT: epicardial fat tissue. Mann-Whitney U, Student t and Fisher's Exact tests. Statistical significance: * *P*<0.05, ** *P*<0.001

The Pearson correlation analysis showed a statistically significant correlation between EFT thickness and C-peptide (*P*=0.002, r=0.460). EFT thickness was further correlated with age (*P*=0.008, r=0.397), weight (*P*=0.042, r=0.308), and waist circumference (*P*=0.035, r= 0.318) (Table 2). Serum fasting C-peptide levels were significantly correlated with triglycerides (*P*=0.023, r= -0.288) among the metabolic syndrome parameters (Table 3).

Table 2: Correlation of epicardial fat tissue thickness with other parameters

		Epicardial fat tissue
Age (years)	r	0.397[a,b]
	P	0.008
Weight (kg)	r	0.308[a]
	P	0.042
WC(cm)	r	0.318
	P	0.035[b]
Insulin (IU/ml)	r	0.111
	P	0.472
C peptide (ng/ml)	r	0.460[a,b]
	P	0.002
HOMA-IR	r	0.152
	P	0.324

[a] Spearman's rho correlation, [b] Pearson correlation, WC: waist circumference

Table 3: Correlations of C-peptide with metabolic syndrome characteristics

		C-peptide
Age (years)	r	0.113
	P	0.381
WC (cm)	r	0.181
	P	0.187
BMI (kg/m2)	r	-0.281
	P	0.032
Fasting glucose (mg/dl)	r	-0.162
	P	0.208
HDL-c (mg/dl)	r	0.236
	P	0.065
TG (mg/dl)	r	-0.288
	P	0.023
SBP (mmHg)	r	-0.021
	P	0.869

WC: waist circumference, BMI: body mass index, HDL-c: High density lipoprotein cholesterol, TG: Triglycerides, SBP: systolic blood pressure

Discussion

The prevalence of metabolic syndrome has gradually increased in the past decades, which brings cardio-metabolic and cardiovascular risks. In most countries, the prevalence of MetS ranges between 20% to %30 in the adult population, depending on the criteria [1]. Besides dyslipidemia, hyperglycemia, and hypertension, the patients with MetS are under the threat of increased proinflammatory and prothrombotic states. According to the International Diabetes foundation (IDF), patients with MetS have five-times increased risk for type 2 diabetes and 3 times increased risk for myocardial infarction or stroke [9].

In our study, we found high serum C-peptide levels in patients with MetS who do not have any cardiovascular event history. Studies showed that MetS is strongly associated with inflammation, insulin sensitivity, endothelial dysfunction, and oxidative stress [10-11]. To identify the presence and progression of these factors in MetS, several circulating factors including dyslipidemia components, C-peptide, bilirubin, fibrinogen, uric acid, reactive oxygen species, antioxidants were studied [12]. Although the exact mechanism remains unclear, C-peptide was suggested as an indicator of insulin resistance by two possible pathways. First, the elevated levels of pro-inflammatory cytokines in muscle tissue promotes the increase of triglycerides and insulin resistance by the regulatory effect of C-peptide [13]. Second, inactive hexamer insulin may be activated by the presence of C-peptide, which further increases glucose utilization [14]. We found no correlations between C-peptide and HOMA-IR in our patient group, which can be explained by the ongoing antidiabetic treatment of the patients with type 2 diabetes.

Among the metabolic syndrome parameters, we found that C-peptide was closely associated with serum triglyceride level only. Marx et al. showed that in patients with diabetes, C-peptide may cause early atherosclerotic lesions to progress through a collection of inflammatory cells and proliferation of

smooth muscle cells [15]. However, Patel et al. [16] suggested that fasting serum C-peptide levels predict cardiovascular and overall death better than serum insulin and its derived measures of insulin resistance, even in the non-diabetic population. Similar results in the literature suggest that C-peptide is a predictor of cardiovascular disease and overall mortality, possibly due to the increase atherogenic factors [17].

Epicardial fat tissue is normally present in humans and mammals. In lean humans it has been shown to express and secrete beneficial cytokines like adiponectin, which have vasodilatory properties [18]. However, in the presence of cardio-metabolic disorders like insulin resistance and obesity, adiponectin decreases and TNF-α increases, which leads up to arterial vasoconstriction, inflammation, and endothelial dysfunction [19]. EFT is thought to interact with coronary arteries by secreting cytokines to the interstitial fluid, the arterial wall and finally the endothelium. Besides this paracrine effect, it is hypothesized that EFT releases free fatty acids and cytokines directly into the vaso vasorum, which is called the vasocrine effect [20]. In previous reports, EFT was reported as an independent risk factor for athero-thrombotic cardiac events [21]. Furthermore, EFT thickness measurement was suggested as a predictive tool, even for the assessment of asymptomatic individuals [22]. In this report, the mean EFT thickness was 0.63 (0.22) mm in patients with metabolic syndrome, which was significantly higher than that in healthy controls. Although some studies revealed the relationship between EFT, insulin and HOMA-IR, the mechanism of interactions with glucose metabolism remains unclear [21]. We found no correlations between HOMA-IR and EFT thickness; however, a positive correlation existed between C-peptide and EFT thickness.

Visceral adipose tissue and EFT serve as a buffer for free fatty acids in metabolically healthy individuals. In the presence of obesity and type 2 diabetes, they both become thicker and dysfunctional [23]. It is noteworthy that the volume of visceral adipose tissue correlates with the volume of EFT, and thus, echocardiographic assessment has a crucial role in the cardiovascular risk assessment of patients with MetS and obesity [24]. Recent studies on the patients with MetS showed that EFT thickness could be a better indicator of visceral obesity rather than waist circumference [25]. Our study revealed that EFT thickness was positively correlated with waist circumference but did not correlate with other indices of obesity.

The major aim of the present report is to clarify the association of C-peptide with EFT. The determined correlation between C-peptide and EFT suggests that C-peptide could be used as a laboratory indicator of EFT thickness, which gives an insight about the cardio-metabolic risk of the patients with metabolic syndrome. Moreover, recent studies demonstrate the regulatory role of C-peptide on low-grade inflammation and its biological importance [26].

This study has some limitations. First, postprandial C-peptide levels were not included. Second, the ongoing antidiabetic, antihypertensive treatment of the patients in metabolic syndrome group caused an underestimation of the correlations considering insulin, HOMA-IR and C-peptide and blood pressure. Third, due to cross-sectional design of the study, a causal relationship could not be determined.

Conclusion

In this study, we determined high levels of serum fasting C-peptide and increased EFT thickness in patients with MetS. Furthermore, a clear positive association was found between C-peptide and EFT thickness in patients of MetS. However, longstanding observational studies are needed to understand the value of both C-peptide and EFT thickness measurement in predicting cardiovascular events in MetS.

References

1. Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol. 2008;28(4):629-36. doi: 10.1161/ATVBAHA.107.151092.
2. Sherling DH, Perumareddi P, Hennekens CH. Metabolic Syndrome. J Cardiovasc Pharmacol Ther. 2017;22(4):365-7. doi: 10.1177/1074248416686187.
3. Robberecht H, Bruyne T, Hermans N. Biomarkers of the metabolic syndrome: Influence of minerals, oligo- and trace elements. J Trace Elem Med Biol. 2017;43:23-8. doi: 10.1016/j.jtemb.2016.10.005.
4. Kim BY, Jung CH, Mok JO, Kang SK, Kim CH. Association between serum C-peptide levels and chronic microvascular complications in Korean type 2 diabetic patients. Acta Diabetol. 2012;49(1):9-15. doi: 10.1007/s00592-010-0249-6.
5. Fitzgibbons TP, Czech MP. Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations. J Am Heart Assoc. 2014;3(2):e000582. doi: 10.1161/JAHA.113.000582. PMID: 24595191; PMCID: PMC4187500.
6. Baragetti A, Pisano G, Bertelli C, Garlaschelli K, Grigore L, Fracanzani AL, et al. Subclinical atherosclerosis is associated with Epicardial Fat Thickness and hepatic steatosis in the general population. Nutr Metab Cardiovasc Dis. 2016;26(2):141-53. doi: 10.1016/j.numecd.2015.10.013. Epub 2015 Nov 2. PMID: 26777475.
7. National Cholesterol Education Program. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final report. Circulation. 2002;106:3143–21. PMID:12485966.
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9. doi: 10.1007/BF00280883. PMID: 3899825.
9. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. International Diabetes Federation Task Force on Epidemiology and Prevention; Hational Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5. doi: 10.1161/CIRCULATIONAHA.109.192644. Epub 2009 Oct 5. PMID: 19805654.
10. Festa A, D'Agostino R Jr, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation. 2000;102(1):42-7. doi: 10.1161/01.cir.102.1.42. PMID: 10880413.
11. Lann D, LeRoith D. Insulin resistance as the underlying cause for the metabolic syndrome. Med Clin North Am. 2007;91(6):1063-77. doi:10.1016/j.mcna.2007.06.012
12. Robberecht H, Hermans N. Biomarkers of Metabolic Syndrome: Biochemical Background and Clinical Significance. Metab Syndr Relat Disord. 2016;14(2):47-93. doi: 10.1089/met.2015.0113.
13. Fuentes E, Guzmán-Jofre L, Moore-Carrasco R, Palomo I. Role of PPARs in inflammatory processes associated with metabolic syndrome (Review). Mol Med Rep. 2013;8(6):1611-6. doi: 10.3892/mmr.2013.1714. Epub 2013 Oct 7. PMID: 24100795
14. Shafqat J, Melles E, Sigmundsson K, Johansson BL, Ekberg K, Alvelius G, et al. Proinsulin C-peptide elicits disaggregation of insulin resulting in enhanced physiological insulin effects. Cell Mol Life Sci. 2006;63(15):1805-11. doi: 10.1007/s00018-006-6204-6. PMID: 16845606; PMCID: PMC2773842.
15. Marx N, Walcher D, Raichle C, Aleksic M, Bach H, Grub M et al. C-peptide colocalizes with macrophages in early arteriosclerotic lesions of diabetic subjects and induces monocyte chemotaxis in vitro. Arterioscler Thromb Vasc Biol. 2004;24(3):540-5. doi:10.1161/01.ATV.0000116027.81513.68
16. Patel N, Taveira TH, Choudhary G, Whitlatch H, Wu WC. Fasting serum C-peptide levels predict cardiovascular and overall death in nondiabetic adults. J Am Heart Assoc. 2012;1(6):e003152. doi: 10.1161/JAHA.112.003152.
17. Li Y, Zhao D, Li Y, Meng L, Enwer G. Serum C-peptide as a key contributor to lipid-related residual cardiovascular risk in the elderly. Arch Gerontol Geriatr. 2017;73:263-268. doi: 10.1016/j.archger.2017.05.018.
18. Henrichot E, Juge-Aubry CE, Pernin A, Pache JC, Velebit V, Dayer JM, et al. Production of chemokines by perivascular adipose tissue: a role in the pathogenesis of atherosclerosis?. Arterioscler Thromb Vasc Biol. 2005;25(12):2594–2599. doi:10.1161/01.ATV.0000188508.40052.35
19. Fitzgibbons TP, Czech MP. Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations. J Am Heart Assoc. 2014;3(2):e000582. doi:10.1161/JAHA.113.000582
20. Ansaldo AM, Montecucco F, Sahebkar A, Dallegri F, Carbone F. Epicardial adipose tissue and cardiovascular diseases. Int J Cardiol. 2019;278:254-260. doi: 10.1016/j.ijcard.2018.09.089. Epub 2018 Oct 1. PMID: 30297191
21. Versteylen MO, Takx RA, Joosen IA, Nelemans PJ, Das M,Crijns HJ, et al. Epicardial adipose tissue volume as a predictor for coronary artery disease in diabetic, impaired fasting glucose, and non-diabetic patients presenting with chest pain. Eur Heart J Cardiovasc Imaging. 2012;13(6):517–523. doi:10.1093/ehjci/jes024.
22. Bachar GN, Dicker D, Kornowski R, Atar E. Epicardial adipose tissue as a predictor of coronary artery disease in asymptomatic subjects. Am J Cardiol. 2012;110(4):534–538. doi:10.1016/j.amjcard.2012.04.024
23. Iacobellis G, Singh N, Wharton S, Sharma AM. Substantial changes in epicardial fat thickness after weight loss in severely obese subjects. Obesity (Silver Spring). 2008;16(7):1693-7. doi: 10.1038/oby.2008.251. Epub 2008 May 1. PMID: 18451775.
24. González N, Moreno-Villegas Z, González-Bris A, Egido J, Lorenzo Ó. Regulation of visceral and epicardial adipose tissue for preventing cardiovascular injuries associated to obesity and diabetes. Cardiovasc Diabetol. 2017;16(1):44. doi: 10.1186/s12933-017-0528-4. PMID: 28376896; PMCID: PMC5379721.

25. Akyol B, Boyraz M, Aysoy C. Relationship of epicardial adipose tissue thickness with early indicators of atherosclerosis and cardiac functional changes in obese adolescents with metabolic syndrome. J Clin Res Pediatr Endocrinol 2013;5:156-163.
26. Wahren J, Larsson C. C-peptide: new findings and therapeutic possibilities. Diabetes Res Clin Pract. 2015;107(3):309-19. doi: 10.1016/j.diabres.2015.01.016.

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Comparison of excision and primary closure vs. crystallized phenol treatment in pilonidal sinus disease: A comparative retrospective study

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Abstract

Background/Aim: Pilonidal sinus is an inflammatory condition that affects the intergluteal sulcus. Since there is no standard treatment for pilonidal sinus, comparative studies are needed. Our study aimed to comparatively evaluate the treatment success, postoperative complications and recurrence in excision/primary repair surgery and crystallized phenol application in pilonidal sinus disease.

Methods: A total of 376 pilonidal sinus patients over the age of 18 years who visited our general surgery clinic between January 2017-January 2020 were included in this retrospective cohort study. They were divided into two groups based on whether they underwent phenol treatment or surgery. The patients' age, body mass index (BMI), gender, number of pits, length of stay in the hospital, return to normal life, mean follow-up times, complications, and satisfaction data were recorded. At the end of the follow-up period, all patients were contacted by telephone and the recurrence rates were noted.

Results: Both groups were similar in terms of age, gender, and BMI (P>0.05 for all). The mean age of 374 patients included in the study was 23.38 (4.9) years. The mean follow-up time was 25.47 months. Patients in the crystallized phenol group did not require hospitalization. In the primary repair group, the median length of hospital stay was 1.15 days. Complications such as wound infection, hematoma, and wound dehiscence were significantly less in the phenol group. The recurrence rates in the phenol and primary repair groups were 8% and 10%, respectively (P=0.326). Return to normal life was significantly faster in the phenol group. The success rate in the phenol group was 92%.

Conclusion: Although the recurrence rates are similar, crystallized phenol therapy is superior to primary repair due to better wound healing rates, ease of application, and fewer complication rates. More than one application is recommended in phenol treatment.

Keywords: Pilonidal sinus disease, Crystallized phenol, Primary repair

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Introduction

Treatments for pilonidal sinus disease (PSD) are generally insufficient. Although many treatment modalities have been described for PSD, rapid recovery, minimal patient discomfort, and low recurrence rates are still not achieved [1,2]. There are many studies comparing various treatment methods, but the results obtained are inconsistent [3-7].

Anderson was the first to perform surgery in 1847 [8]. The first phenol application was made with liquid phenol in 1964, and solid phenol was later considered more appropriate due to high recurrence rates with the use of liquid form [9, 10].

Crystalline phenol is a normally solid agent that becomes liquid with body temperature. Apart from sclerosing the pilonidal sinus tract, it also has anesthetic and antiseptic properties. After administration, it irritates the tissue, contributes to the formation of granulation tissue, and causes healing with fibrosis [11, 12]. Studies conducted in recent years showed that better results were obtained with the application of flap techniques in surgery compared to primary excision methods. However, primary excision continues to be performed frequently in most centers [11, 13].

The aim of our study is to show the usability of the easily accessible phenol treatment in centers that currently perform excision and primary closure surgery, as well as evaluate the results of primary closure.

Materials and methods

After the approval of the Keçiören Training and Research Hospital Clinical Research Ethics Committee (08.12.2020) was obtained with the decision number 2012-KAEK-15/2201, our study was conducted retrospectively per the Helsinki declaration, and written informed consent was obtained from all patients. A total of 526 PDS patients over the age of 18 years who presented to the general surgery clinic between January 2017-January 2020 were included in the study. Patients with recurrent pilonidal sinus disease an unavailable data, those who underwent other surgical procedures for pilonidal sinus, patients with chronic diseases (diabetes, hypertension, etc.) that impair wound healing, a history of radiotherapy to the pelvic region, malignity, those under steroid therapy, patients with coagulopathy, drug allergy, complicated PSD and abscess were excluded from the study. A total of 376 patients with complete data who fulfilled the criteria were included.

Age, gender, number of pits, postoperative complications (wound dehiscence, infection, and hematoma), length of hospital stay, and body mass index (BMI) were recorded from the patient files and the hospital information system. The number of times the patients underwent phenol treatment was noted. Then, the 2-year recurrence rates of all patients were inquired via telephone, computer records, or during follow-ups. The patients were divided into two as those who received the phenol treatment or primary closure.

Phenol treatment

After sterilization of the area around the pilonidal sinus, local anesthesia was achieved with peripheral nerve block and filtration anesthesia using lidocaine (concentration 20 mg/ml). All hairs in the sinus tract were removed.

The area to be treated and its surroundings were protected with an antibiotic cream so that it would not be damaged during the phenol application. In this process, antibiotic-free creams that reduce irritation and burning effect can also be used. The sinus opening was expanded with mosquito clippers if it was less than 3 mm wide. A surgical curette was used to clean the sinus tract. Then, approximately 5-6 grams of phenol was administered to the tract three times. The procedure was terminated by dressing. A follow-up clinical examination was performed 10 days later. No extra procedures were performed to the patients whose sinuses were completely closed. Phenol application was continued for a maximum of 3 times in patients with open sinus tracts. The closure of the cavity and the absence of discharge were considered cure. The creation of new sinus orifices after healing was defined as recurrence.

Surgical procedure

The patients were operated in the prone position with local anesthesia under local operating room conditions. Local anesthesia was achieved with peripheral nerve block and filtration anesthesia using lidocaine (concentration 20 mg/ml). Methylene blue was injected into the tract to show the boundaries. After primary excision was completed, the layers were closed primarily. The closure of the cavity and the absence of discharge were considered cure. The occurrence of new sinus orifices after healing was defined as recurrence.

Statistical analysis

Data analysis was performed using SPSS for Windows 22 (Chicago, IL, USA) package program. The Kolmogorov-Smirnov test was performed to test whether the data were normally distributed. Categorical variables were presented with frequency distribution (numbers and percentages) and descriptive statistics were used for numerical variables. The Mann-Whitney U test was used to assess differences in numerical variables between the groups, and the Chi-square test was used to compare categorical variables. A *P*-value of <0.05 was considered significant.

Results

The mean age of 374 participants was 23.38 (4.9) years (range: 18-54 years). The average time of follow-up was 25.47 months (range: 20-35 months). Table 1 shows the demographic features of the patients.

Table 1: The demographic characteristics and findings according to the treatment groups

	Crystallized phenol group (n=187)	Simple primary closure group (n=188)	*P*-value
Age, y, mean (SD)	24.83(4.77)	24.44(3.91)	0.664*
BMI, kg/m^2	23.21(3.14)	22.87(2.78)	0.316*
Gender, n, (%)			
Male	123(65.77%)	131(69.68%)	
Female	64 (34.23%)	57(30.32%)	
Length of hospital stay, d, median(range)	0	1.15(0-5)	<0.001*
Complications, n (%)	3(1.6%)	69(36.65%)	<0.001†
Wound infection	3(1.6%)	32(17.02%)	
Hematoma	0	23(12.23%)	
Wound dehiscence	0	14 (7.4%)	
Back to normal life, d median (range)	1(1-20)	5(1-40)	<0.001*
Recurrence, n (%)	15 (%8)	19 (%10)	†0.326
Follow-up, mean (range)	25.19(20-35)	25.75(22-30)	*0.110
Number of phenol applications			
1	69(36.89%)	0	
2	85(45.46%)	0	
3	33(17.65%)	0	

*Mann-Whitney U test, †chi-square test, BMI: Body mass index

In terms of age, gender, BMI, recurrence, and follow-up duration, there was no significant difference between the groups (Table 1). In the primary closure group, the length of hospital stay was significantly longer (P<0.001). Patients in the crystallized phenol group did not require hospitalization. In the primary closure group, the median length of hospital stay was 1.15 days (median, 0-5 days).

However, complications such as wound infection, hematoma, and wound dehiscence were significantly less common in the phenol group (P<0.001). While complications were observed in 3 (1.6%) patients in the phenol group, wound infection also occurred in these three patients. Complications were observed in a total of 69 (36.65%) patients in the primary closure group. Wound infection was observed in 32 (17.02%) patients, hematoma in 23 (12.23%) patients, and wound dehiscence in 14 (7.4%) patients.

The recurrence rates in the phenol and primary closure groups were 15 (8%) and 19 (10%), respectively (P=0.326). Return to normal life was significantly faster in the phenol group (P<0.001).

Discussion

PDS is frequently observed in the sacrococcygeal region. Having a hairy body structure, excessive daily hair loss, deep and narrow gluteal cleft, the long stay of the hair in this cleft, humidity, weight, sitting for a long time and poor hygiene are predisposing factors for PDS [14]. There are many treatment methods for pilonidal sinus disease, which range from a minimally invasive method to complex flap reconstruction. In complex cases, open wounds left to secondary closure and flap methods are preferred. For patients with uncomplicated pilonidal sinus, crystallized phenol and primary closure methods can be used. Although there are not many comparative studies in the literature for these two methods, they are considered advantageous in terms of practicality, fast recovery times, and short operation times [15-17]. In our study, return to normal life was faster in the phenol group. This was thought to be due to the higher rate of wound infection, hematoma, and wound dehiscence in the primary closure group.

Some clinicians do not prefer the open method because of the high recurrence rates. Complications in PDS are important in determining the ideal treatment. However, primary excision and closure can be attempted, as it does not pose a challenge for flap reconstruction in case of reoperation in patients [15, 18]. Significant complications after the primary closure method are wound infection and wound dehiscence. Wound healing problems have been reported at a rate of 11-34% after the primary closure technique [18, 19]. In our study, this rate was 36.65%.

Local anesthesia was administered to all patients in our case series as described in the literature. Spinal anesthesia is required for other complex procedures. Spinal anesthesia is more invasive and expensive and can cause complications such as headache and urinary retention [12].

Different studies in the literature have shown the success rates of crystalline phenol treatment to range from 60% to 100%. [20]. It was discovered that the success rate rose as the phenol treatment was repeated. In the study of Attaallah et al. [21], they showed that complete recovery rate after 16 months of follow-up increased to 76% when phenol was applied once and to 86% with multiple applications. Akan et al. [22] followed 42 patients who underwent phenol treatment once for 26 months and reported a success rate of 88%. This rate ranged between 70-77.7% in the studies of Kayaalp et al. [23] and Sakçak et al. [24]. In addition, as a result of a 54-month follow-up, Aygen et al. [25] found a recovery rate of 91.7% in the phenol treatment, which they applied an average of 3.7 times. In the study of Yuksel, the success rate after 40 months of follow-up was 88% [26]. In our study, the success rate of phenol treatment was 92% after 25 months of follow-up. In some circumstances, it appears that administering two or more phenol treatments is critical to the treatment's success.

In our study, wound site infection was observed in 3 (1.6%) cases. The reason for this is considered to be phenol leakage into the adjacent tissues and the obstruction of the sinus tract [27]. Wound site infection was seen in 69 (36.65%) patients in the surgery group. In terms of complications, the phenol group was superior to the open surgery group.

Even though the two techniques had resembling recurrence and complication rates in prospective randomized controlled research conducted by Sengul et al. [3], crystalline phenol treatment is advised due to advantages such as shorter procedural time and less analgesia requirement. In our study, the recurrence rates were similar, but the phenol group was superior to the surgical group in terms of complications.

Limitations

The retrospective design of our study, short period of follow-up (25 months), and the inclusion of only primary cases can be considered limitations. However, the number of patients is higher than most studies in terms of decision making. It is important that similar techniques are used in a single center and by the same surgeons. Future studies with larger series and more homogeneously paired groups are needed.

Conclusion

In our study, the recurrence rates of phenol treatment and excision/primary closure procedures in PDS were similar. However, phenol treatment has the advantage of low complication rates, easy application, and the advantage of being a minimally invasive method that provides an early return to normal life. In addition, both methods can be used in primary cases under local operating room conditions, since they do not affect subsequent surgical treatments. Although excision/primary repair is an easy-to-apply method under local anesthesia in pilonidal sinus patients, the superiority of phenol application was demonstrated in our study. Prospective randomized controlled studies are needed for more conclusive results.

References

1. Allen-Mersh T. Pilonidal sinus: finding the right track for treatment. Br J Surg. 1990;77:123-32.
2. Yiğit B, Yetkin SG, Çitgez B, Eken KG, Özşahin H. Intermammary pilonidal sinus: A case report of a 23-year-old girl. J Surg Med. 2020;4(2):170-2.
3. Khan N, Singhal P, Chandrashekhar S, Goel D, Patel K, Deshpande N. Is limberg flap better than excision and primary closure for treatment of sacrococcygeal pilonidal sinus: a prospective randomised study of 30 cases. Int Surg J. 2021;8:699-703.
4. Sequeira JB, Coelho A, Marinho AS, Bonet B, Carvalho F, Moreira-Pinto J. Endoscopic pilonidal sinus treatment versus total excision with primary closure for sacrococcygeal pilonidal sinus disease in the pediatric population. J Pediatr Surg. 2018;53:2003-7.
5. Jabbar MS, Bhutta MM, Puri N. Comparison between primary closure with Limberg Flap versus open procedure in treatment of pilonidal sinus, in terms of frequency of post-operative wound infection. Pak J Med Sci. 2018;34:49.

6. Sinnott CJ, Glickman LT. Limberg flap reconstruction for sacrococcygeal pilonidal sinus disease with and without acute abscess: Our experience and a review of the literature. Arch Plast Surg. 2019;46:235.
7. Romaniszyn M, Swirta J, Walega P. Long-term results of endoscopic pilonidal sinus treatment vs Limberg flap for treatment of difficult cases of complicated pilonidal disease: a prospective, nonrandomized study. Colorectal Dis. 2020;22:319-24.
8. Akkurt G, Ataş H. Comparison of Crystallized Phenol Application and the Karydakis Flap Technique in the Treatment of Sacrococcygeally Localized Pilonidal Sinus Disease. Cureus. 2021;13(5):e15030 .
9. Maurice B, Greenwood R. A conservative treatment of pilonidal sinus. Br J Surg. 1964;51:510-2.
10. Dogru O, Camci C, Aygen E, Girgin M, Topuz Ö. Pilonidal Sinus Treated With Crystallized Phenol. Dis Colon Rectum. 2004;47:1934-8.
11. Dag A, Colak T, Turkmenoglu O, Sozutek A, Gundogdu R. Phenol procedure for pilonidal sinus disease and risk factors for treatment failure. Surgery. 2012;151:113-7.
12. Kayaalp C, Olmez A, Aydin C, Piskin T, Kahraman L. Investigation of a one-time phenol application for pilonidal disease. Med Princ Pract. 2010;19:212-5.
13. Tavassoli A, Noorshafiee S, Nazarzadeh R. Comparison of excision with primary repair versus Limberg flap. Int J Surg. 2011;9(4):343-6.
14. Cubukçu A, Carkman S, Gönüllü NN, Alponat A, Kayabaşi B, Eyüboğlu E. Lack of evidence that obesity is a cause of pilonidal sinus disease. Eur J Surg. 2001 Apr;167(4):297-8.
15. Turkoglu A, Bozdag Z, Gumus M, Oguz A, Gul M, Yılmaz A, et al. Comparison of crystallized phenol treatment and simple primary closure methods for pilonidal sinus disease. Int Sur. 2018;103:424-8.
16. Karakayali F, Karagulle E, Karabulut Z, Oksuz E, Moray G, Haberal M. Unroofing and marsupialization vs. rhomboid excision and Limberg flap in pilonidal disease: a prospective, randomized, clinical trial. Dis Colon Rectum. 2009;52:496-502.
17. Roshdy H, Ali Y, Askar W, Awad I, Farid M, Farid M. Rhomboid flap versus primary closure after excision of saccrococcigeal pilonidal sinus (a prospective randomized study). Egypt J Surg. 2010;29:146-52.
18. Al-Jaberi TM. Excision and simple primary closure of chronic pilonidal sinus. Eur J Surg. 2001;167:133-5.
19. Kaya B, Uçtum Y, Şimşek A, Kutaniş R. Treatment of pilonidal sinus with primary closure. A simple and effective method. Turk J Colorectal Dis. 2010;20:59-65.
20. Calikoglu I, Gulpinar K, Oztuna D, Elhan AH, Dogru O, Akyol C, et al. Phenol injection versus excision with open healing in pilonidal disease: a prospective randomized trial. Dis Colon Rectum. 2017;60:161-9.
21. Attaallah W, Coşkın Ş, Coşkun M, Solmaz A, Yeğen C, Gençosmanoğlu R. The impact of crystalline phenol application as a minimal invasive treatment modality for pilonidal sinus disease. Turk J Colorectal Dis. 2015;25:28-33.
22. Akan K, Tihan D, Duman U, Özgün Y, Erol F, Polat M. Comparison of surgical Limberg flap technique and crystallized phenol application in the treatment of pilonidal sinus disease: a retrospective study. Ulus Cerrahi Derg. 2013;29:162.
23. Kayaalp C, Aydin C. Review of phenol treatment in sacrococcygeal pilonidal disease. Tech Coloproctol. 2009;13(3):189-93.
24. Sakçak İ, Avşar FM, Coşgun E. Comparison of the application of low concentration and 80% phenol solution in pilonidal sinus disease. JRSM Short Rep. 2010;1:1-5.
25. Aygen E, Arslan K, Dogru O, Basbug M, Camci C. Crystallized phenol in nonoperative treatment of previously operated, recurrent pilonidal disease. Dis Colon Rectum. 2010;53:932-5.
26. Yuksel ME. Pilonidal sinus disease can be treated with crystallized phenol using a simple three-step technique. Acta Dermatovenerol Alp Pannonica Adriat. 2017;26:15-7.
27. Bayhan Z, Zeren S, Duzgun SA, Ucar BI, Yumun HNA, Mestan M. Crystallized phenol application and modified Limberg flap procedure in treatment of pilonidal sinus disease: A comparative retrospective study. Asian J Surg. 2016;39:172-7.

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Oncoplastic Breast Surgery: Is it reliable in the treatment of multifocal breast cancer? A preliminary report of a prospective randomized controlled trial

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Abstract

Background/Aim: Multifocal breast cancers (MFBCs) still have undiscoverable clinical significance. Being the standard surgical management for early breast cancer, implementation of breast-conservation therapy (BCT) as a surgical procedure for multifocal breast cancers is still questionable and needs a solid basis of clinical evidence via prospective randomized control trials.
Methods: A prospective study was conducted on female patients with operable multifocal breast cancer excluding those diagnosed with inflammatory breast cancer and those to receive neoadjuvant therapy. Surgical management was selected randomly and comprised either modified radical mastectomy (MRM) or different techniques of oncoplastic breast surgery (OPS) with a sealed envelope system based on clinical evaluation and recent guidelines for management at the Surgical Oncology Unit, Alexandria University from May 2017-May 2018. The patients were followed up until February 2021 with a median follow-up of 39 months postoperatively to assess recurrence. Analysis of different clinicopathological factors was performed to evaluate the reliability of OPS in the surgical management of MFBCs.
Results: A total of 132 patients were initially assessed for the eligibility criteria. Finally, 58 patients in the OPS group and 56 patients in the MRM group were followed up until the end of the study period. After a median follow-up of 39 months post-operatively for both groups, three patients belonging to the oncoplastic group suffered from local recurrence (5.2%). Two patients who had MRM had distant recurrence (3.6%). Although recurrence behavior was different between both groups, this was not statistically significant.
Conclusion: OPS is an oncologically safe surgical option for selected cases of multifocal breast cancer.

Keywords: Breast cancer, Multifocal, Recurrence

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Introduction

Multifocal breast cancers (MFBCs) represent a discrete and important oncological issue. The incidence of MFBCs varies from 6% to 60% among breast cancers worldwide [1, 2]. MFBCs are defined when there are two or more synchronous cancerous foci within the same quadrant. The size of the largest tumor focus is considered for the TNM staging system [3].

MFBCs are currently encountered in the surgical oncology field more than in previous decades mostly due to the revolution in the diagnostic modalities of breast cancer. Better guidelines for their management are needed, especially regarding the optimal loco-regional therapy and their impact on survival [4-6].

Being the standard surgical management for early breast cancer, implementation of breast-conservation therapy (BCT) as a surgical procedure for MFBCs is still questionable and needs a solid basis of clinical evidence with prospective randomized control trials [7].

Conventional contraindications to BCT include any clinical conditions which may alter local control and or cosmesis. Multifocal breast cancers may be included in this category [7-10]. However, there is now growing evidence to suggest that oncoplastic conservative surgery (OPS) can be a suitable surgical procedure with acceptable local control rates [11-16].

OPS is divided into the volume-displacement procedure which includes resection with a variable volume of breast tissue, rearrangements, and mammoplasty techniques [7, 8], and volume-replacement procedures, which entails resection with immediate reconstruction using loco-regional flaps [9, 10]. In all cases, simultaneous or delayed correction in the contralateral breast can be done to achieve better symmetry [11].

The present study is directed to analyze, in a prospective series of breast cancer patients treated at a single institution, the reliability of oncoplastic breast conservative surgery as a surgical treatment for selected cases of MFBCs in terms of oncological safety.

Materials and methods

Study design and randomization

In this non-blinded two-arms parallel design randomized clinical trial, multifocal breast cancer patients were first randomly selected by the simple random sampling method. Patients were assessed for eligibility and randomly allocated at a ratio of 1:1 to either the OPS arm or MRM arm using simple randomization by tables of random number generator. Concealed allocation was achieved by sequentially numbered opaque sealed envelopes technique and by keeping the executive of the randomization unaware of study participants' sequence.

Eligibility

Inclusion criteria: Operable female patients with MFBC diagnosed on a clinical and/or radiological basis and proved by core needle who were admitted to the Surgical Oncology Unit, Faculty of Medicine, University of Alexandria.

Exclusion criteria: Patients to receive neoadjuvant treatment or inflammatory carcinoma were excluded because of the tendency towards worse prognosis in the tumor characteristics rather than in the surgical procedure. Also, the method of localization of multifocal disease is a matter of debate [8].

Data collection

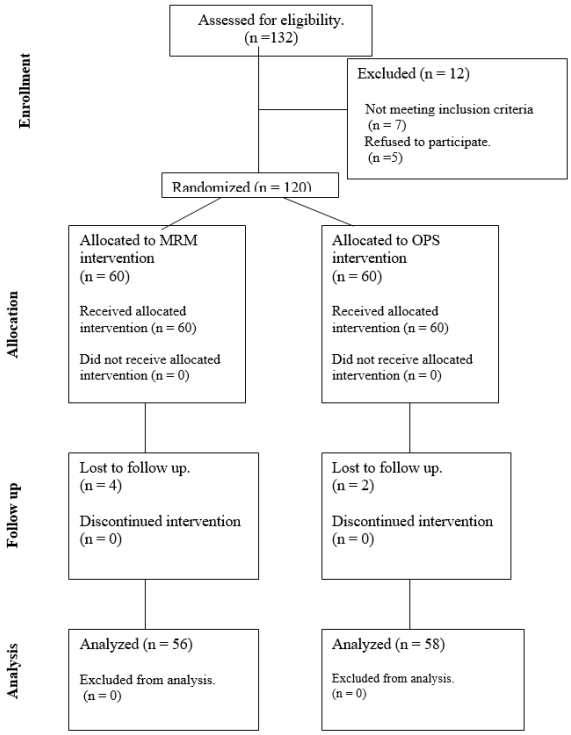
Patients diagnosed as having MFBC signed informed written consent before being enrolled in the study. They were diagnosed as MFBC on clinical and/or mammographic findings. However, MRI was resorted to whenever the mammographic findings were not conclusive (e.g., dense breast, asymmetrical architecture distortion, and lobular carcinoma). Patients were subjected to either total mastectomy or oncoplastic conservative breast surgery according to the arm of the study. Safety margin was assured in the second group by intraoperative pathological assessment. This was performed by the inking of different margins and imprinting of cytological examination of all margins by a dedicated pathologist. Effective communication between the surgeon and the attending pathologist was assured for describing the site and size of the different foci and their relation to each other and concordance with prior imaging studies. Clear margins were defined as no ink on the tumor [8].

Axillary dissection or sentinel node biopsy was performed according to the clinical and radiological states of the axilla.

Patients who underwent total mastectomy were offered different options for immediate reconstruction, only 3 (5.35%) out of 56 patients of the mastectomy accepted immediate reconstruction in the form of autologous pedicled transverse rectus abdominis muscle flap (TRAM flap) to avoid a second surgery.

The CONSORT diagram shows the flow of participants through each stage of the randomized trial (Figure 1).

Figure 1: The CONSORT diagram



After surgical intervention, the following data were recorded:

- **Tumor characteristics:** Size, nodal status, presence of lymphovascular invasion, amount of intraductal component, tumor grade, margin status, hormone receptor, and Her2 status.

- **Rate of re-excision:** If needed, was based on permanent histopathological examination of the excised specimen in patients who underwent OPS.
- **Postoperative surgical complications** or any other procedure-related problems.

All patients were scheduled for clinical follow-up every 6 months with an overall follow-up period of 39 months.

- A mammogram (or ultrasonographic examination of the mastectomy bed) and metastatic workup survey/year. The occurrence of loco-regional recurrence and distant metastases during the follow-up period were documented.

Outcomes

1. Loco-regional recurrence or distant metastases during the follow-up period.
   - Local recurrence is defined as recurrence in the original tumor bed of OPS or the mastectomy field.
   - Regional recurrence refers to metastatic disease in the ipsilateral axilla or supraclavicular lymph nodes or ipsilateral involvement of internal mammary nodes.
2. The disease-free survival of patients was estimated using the Kaplan-Meier method.

Sample size calculation

Previous studies illustrated an overall survival of 94% vs. 90% among patients undergoing breast conservation relative to the group treated with mastectomy, respectively, with no significant difference [17]. If there is truly no difference between the standard and experimental treatment (around 94% in both groups), then 110 patients (55 per each intervention arm) are needed to be 95% sure that the limits of a two-sided 95% confidence interval will exclude a difference between the standard and experimental group of more than 15%. The calculation was based on the following formula for equivalence trial to achieve 80% power at 0.05 significance level:

Calculation based on the formula [18]:

$$n = 2 \times f(\alpha, \beta/2) \times \pi \times (100 - \pi) / d^2$$

where π is the true percent "success" in both the control and experimental treatment groups, and

$$f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$$

where Φ^{-1} is the cumulative distribution function of a standardized normal deviate. We anticipated a potential loss of follow-up of 10%. To account for this, we initially enrolled 132 patients in the trial.

Ethical consideration

The study was approved by the ethical committee of the Faculty of Medicine, University of Alexandria. Also, the study was registered in clinicaltrials.gov (NCT03900299).

https://clinicaltrials.gov/ct2/show/NCT03900299?recrs=d&cond=Breast+Cancer&cntry=EG&draw=2&rank=2

The patients' records were kept confidential and all signed informed consent forms.

Statistical analysis

Data are expressed as mean (SD), and numbers or percentages where appropriate. The Chi-square test was performed to study the significant associations between categorical variables. Fischer exact significance, as well as Monte-Carlo significance, were used if more than 20% of the total expected cell counts <5 at 0.05 level of significance. Kaplan-Meier survival analysis was conducted to compare overall survival and recurrence-free survival outcomes between the two interventions using the Log-rank test. All statistical tests were judged at a 0.05 significance level using IBM SPSS statistics program version 21.

Results

A total of 132 patients were initially assessed for eligibility. Twelve patients were excluded, five refused to participate after enrollment, and 7 patients did not meet the eligibility criteria. Sixty patients were randomized, and 2 patients in the OPS group and 4 patients in the MRM group were lost to follow-up. Finally, 58 patients who were subjected to OPS and 56 patients who underwent MRM continued follow-up (CONSORT diagram).

A summary of the clinicopathological characteristics of patients is given in Table 1. Both groups were similar regarding their age, stage, tumor size, histopathological type, grade, and lymphovascular invasion, presence of excessive intraductal component, hormonal status & Her2 expression.

The adjuvant treatments administered in both groups, whether chemotherapy, radiotherapy, or hormonal, is illustrated in Table 1.

Table 1: A summary of the clinicopathological characteristics of patients

Item		OPS (n=58)		MRM (n=56)		X^2	*P*-value
		No	%	No	%		
Age in years	<40	5	8.6%	3	5.4%	4.011	^{MC}P=0.265
	40-	18	31.0%	10	17.9%		
	50-	14	24.1%	14	25.0%		
	60+	21	36.2%	29	51.8%		
T staging	T1	34	58.6%	23	41.1%	4.139	^{MC}P=0.075
	T2	24	41.4%	32	57.1%		
	T3	0	0.0%	1	1.8%		
N staging	N0	32	55.2%	26	46.4%	0.872	0.351
	N1	26	44.8%	30	53.6%		
	N2	0	0.0%	0	0.0%		
STAGE	I	21	36.2%	12	21.4%	3.773	^{MC}P=0.100
	II	37	63.8%	43	76.8%		
	III	0	0.0%	1	1.8%		
Histopathology	IDC	58	100.0%	55	98.2%	1.045	0.491
	Mucoid	0	0.0%	1	1.8%		
GRADE	II	57	98.3	56	100.0	0.947	1.000
	III	1	1.7	0	0.0		
Estrogen	-ve	6	10.3%	3	5.4%	5.794	^{MC}P=0.123
	+	5	8.6%	11	19.6%		
	++	18	31.0%	23	41.1%		
	+++	29	50.0%	19	33.9%		
Progesterone	-ve	7	12.1%	7	12.5%	0.332	0.954
	+	10	17.2%	11	19.6%		
	++	32	55.2%	28	50.0%		
	+++	9	15.5%	10	17.9%		
HER2	-ve	54	93.1%	51	92.7%	2.289	^{MC}P=0.555
	+	1	1.7%	3	5.5%		
	++	1	1.7%	0	0.0%		
	+++	2	3.4%	1	1.8%		
Intra ductal component	No	47	81.0%	37	66.1%	3.290	0.070
	Yes	11	19.0%	19	33.9%		
LVI	No	26	44.8%	28	50.0%	0.306	0.580
	Yes	32	55.2%	28	50.0%		
POS CHM	No	0	0.0%	2	3.6%	2.108	^{FE}P=
	Yes	58	100.0%	54	96.4%		0.239
POS XRT	No	0	0.0%	2	3.6%	2.108	^{FE}P=
	Yes	58	100.0%	54	96.4%		0.239
POS HOR	No	2	3.4%	1	1.8%	0.307	^{FE}P=1.000
	Yes	56	96.6%	55	98.2%		

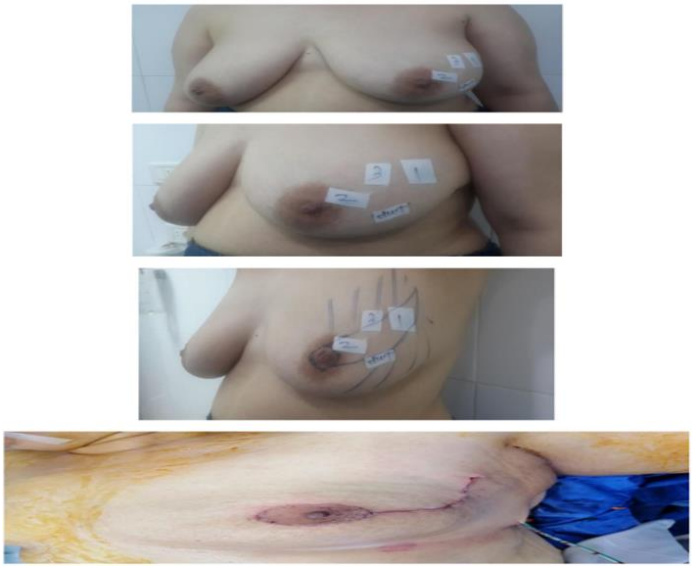
* Chi-square test, ^{FE}P: Fisher exact probability, * P<0.01 (highly significant), ^{MC}P: Monte Carlo exact probability, ** P<0.05 (significant)

Regarding patients who had OPS: Various oncoplastic techniques were utilized (Table 2). Lateral therapeutic mammoplasty was the commonest technique adopted; it was used in 20 patients (34.48%) who had tumors located in the upper outer quadrant (Figure 2).

Table 2: Oncoplastic techniques used in the study

OPS	Tumor location	Number of cases
Lateral therapeutic mammoplasty	Upper outer quadrant	20(34.48%)
Round block	Upper outer quadrant Lower inner quadrant Lower outer quadrant Upper inner quadrant Upper pole	14(24.13%)
Parallelogram lumpectomy	Upper outer quadrant Upper pole Upper inner quadrant	9(15.51%)
J therapeutic mammoplasty	Lower pole	4(6.89%)
V therapeutic mammoplasty	Lower outer quadrant Lower inner quadrant	4(6.89%)
LD FLAP	upper outer quadrant	3(5.17%)
Reduction therapeutic mammoplasty	Upper outer quadrant Upper inner quadrant	2(3.44%)
Grisotti flap	Central (retro areolar)	2(3.44%)

Figure 2: Pre-operative markings of therapeutic lateral mammoplasty and outcome after the remodeling of breast tissue.



Five patients (8.6%) required re-excision after frozen section examination of the excised specimen margins. The results of the margin assessment were confirmed on the final examination of the permanent paraffin block.

Postoperative complications were encountered in 33.92% and 31.03% in the MRM & OPS groups, respectively. They were diverse, related to the nature of the procedure performed, and statistically not significant with P=0.90 for early complications and P=0.57 for late complications (Table 3).

Table 3: Postoperative complications after OPS and MRM

	MRM (n=56)	OPS (n=58)	*P*-value
Early complications			0.900
Hematoma	2(3.57%)	1(1.72%)	
Seroma	11(19.64%)	8(13.79%)	
Abscess	1(1.78%)	2(3.44%)	
Skin or Flap necrosis	2(3.57%)	2(3.44%)	
Total no of complications	16(28.57%)	13(22.41%)	
No complications	40(71.42%)	45(77.59%)	
Late complications			0.579
Scar fibrosis	1(1.78%)	1(1.7%)	
Keloid	2(3.57%)	2(3.44%)	
Steatonecrosis	0	2(3.44%)	
Total no of complications	3(5.35%)	5(8.62%)	
No complications	53(94.65%)	53(91.38%)	

After a median follow-up period of 39 months, three patients belonging to the oncoplastic group suffered from local recurrence (5.2%) and two patients who had MRM had distant recurrence (3.6%). Although the recurrence pattern differed between the two groups, local recurrence, distant recurrence, and the overall recurrence rates were not significant (P=0.244, P=0.239, P=0.671, HR: 1.474 at 95% CI, respectively) (Table 4, 5).

Table 4: univariate analysis of local and distant recurrence in both groups

Item		Surgery OPS (n= 58) No	%	MRM (n= 56) No	%	X^2	*P*-value
Recurrence	No	55	94.8%	54	96.4%	0.174	^{FE}P=1.000
	Local	3	5.2%	0	0.0%	2.975	^{FE}P=0.244
	Distant	0	0.0%	2	3.6%	2.108	^{FE}P=0.239

Table 5: Rate of recurrence in both groups

	No Recurrence No	%	Recurrence No	%	*P*-value	HR (95%C.I)
OPS	55	94.8%	3	5.2%	0.671	1.474 (0.246 – 8.820)
MRM	54	96.4%	2	3.6%		1.000

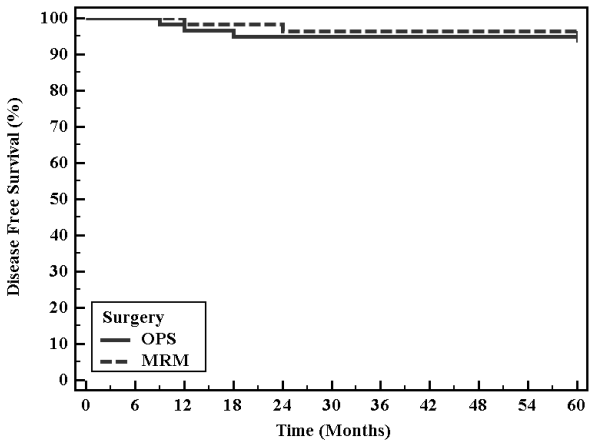
HR: Hazard ratio, CI: Confidence interval, LL: Lower limit, UL: Upper Limit

The Kaplan-Meier method revealed the disease-free survival (DFS) to be 94.8% and 96.4% in OPS & MRM groups, respectively. This difference was not significant (Figure 3, Table 6).

Table 6: Kaplan-Meier survival analysis for disease-free survival with surgery

	Mean	% 1 year	% End of study	Log-rank χ^2	*P*-value
Surgery					
OPS	57.57	96.6	94.8	0.183	0.668
MRM	58.50	98.2	96.4		

Figure 3: Kaplan-Meier survival curve for disease-free survival with surgery



Discussion

Multifocal breast cancer is an entity that needs consideration. Its biological basis is not well understood, especially whether it is the result of a simultaneous overgrowth of tumor foci or an outcome of extensive intraductal carcinoma [19]. Many studies found it to have a different clinical outcome with a poorer prognosis if compared with unifocal breast cancer of the same stage [20with This is attributed to the high invasive tumor burden and association with lymph node metastases [21]. The reported association between multifocality and the outcome of patients in early breast cancer is variable [20, 22, 23]. It has a higher possibility of recurrence and adverse survival after surgical treatment, especially if breast conservative surgery is performed. This paradox directed many surgeons to perform mastectomy for these patients [24, 25]. This was the reported trend in the past two decades [9, 10, 24, 26]. Recently, some studies found a lower incidence of local recurrence in patients with multifocal breast cancer treated with breast conservative surgery [27, 28]. However, most were retrospective.

Thus, the present study was conducted prospectively to compare the results of mastectomy and breast conservative therapy in the treatment of multifocal breast cancer. We included only MFBC patients diagnosed on a clinical and radiological basis. The pattern of recurrence was different between both groups; local recurrence only occurred in patients who

underwent OPS while patients who underwent MRM suffered only from distant recurrence. The overall recurrence rate and the disease-free survival (DFS) were not significantly different between the two groups.

Reviewing the literature, few studies were found investigating breast conservative therapy (BCT) and mastectomy as treatment options for MFBC. The majority found no difference between both modalities regarding local recurrence (LR) and disease-free survival (DFS) [17, 29]. Moreover, Wolters et al. found that BCT and mastectomy are suitable comparable choices in the surgical treatment of T1/2 MFBC [14]. These previous results are in agreement with our work. One of the strengths of our study is that we determined the eligibility criteria for inclusion and exclusion of patients like everyday clinical practice while applying both interventions, so the findings from this study could be generalizable. We encountered the most clinically important outcomes, and we also considered the potential complications after surgery.

Although the follow-up period in our study is relatively short, the paucity of prospective RCT addressing MFBC encouraged the authors to publish the results as a preliminary study with early results. Still, longer follow-up periods are needed. However, this study has the advantage of being a prospective one.

Conclusions

From the present work, we can conclude that breast OPS is a safe option to treat selected cases of MFBC that can, nowadays, is better characterized with the wide use of magnetic resonance mammography. It achieves a wide resection margin enabling the removal of all tumor foci.

References

1. Yerushalmi R, Kennecke H, Woods R, Olivotto IA, Speers C, Gelmon KA. Does multicentric/multifocal breast cancer differ from unifocal breast cancer? An analysis of survival and contralateral breast cancer incidence. Breast Cancer Res Treat. 2009;117:365-70.
2. Mona P Tan, Nadya Y Sitoh, Yih Yiow Sitoh. Optimizing breast conservation treatment for multifocal and multicentric breast cancer: A Worthwhile Endeavour? World J Surg. 2016;40:315-22.
3. Van la Parra RF, de Roos WK, Constant CM, Bavelaar-Croon C D, Barneveld P C, Bosscha K. A prospective validation study of sentinel lymph node biopsy in multicentric breast cancer. SMMaC trial. Eur J Surg Oncol. 2014;40:1250-5.
4. Wilkinson LS, Given-Wilson R, Hall T, Potts H, Sharma AK, Smith E. Increasing the diagnosis of multifocal primary breast cancer by the use of bilateral whole-breast ultrasound. Clin Radiol. 2005;60:573-8.
5. Sardanelli F, Giuseppetti GM, Panizza P, Bazzocchi M, Fausto A, Simonetti G, et al. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in Fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol. 2004;183:1149-57.
6. Houssami N, Ciatto S, Macaskill P, Lord SJ, Warren RM, Dixon JM, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: Systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. 2008;26:3248-58.
7. John R Benson, Ismail Jatoi, Masakazu Toi. Surgical management of multiple ipsilateral breast cancers. Future Oncol. 2019;15:1185-91.
8. NCCN guidelines at : https://www.nccn.org/professionals/physician_gls/default.aspx accessed at May 2018
9. Matthijs V. Nijenhuis, Emiel J.Th. Rutgers.Conservative surgery for multifocal/multicentric breast cancer. The Breast. 2015;24:S96-99.
10. Wilson LD, Beinfield M, McKhamn CF, Haffty BG. Conservative surgery and radiation in the treatment of synchronous ipsilateral breast cancers. Cancer. 1993;72:137-42.
11. Bauman L, Barth RJ, Rosenkranz KM. Breast conservation in women with multifocal-multicentric breast cancer: is it feasible? Ann Surg Oncol. 2010;17:S325-9.
12. Kapoor NM, Chung A, Huynh K, Giuliano AE. Preliminary results: double lumpectomies for multicentric breast cancer. Am Surg. 2012;78:1345-8.
13. Ustaalioglu BO, Bilici A, Kefeli U, Şeker M, Oncel M, Gezen C, et al. The importance of multifocal/multicentric tumor on the disease-free survival of breast cancer patients. Am J Clin Oncol. 2012;35:580-6.
14. Wolters R, Wöckel A, Janni W, Novopashenny I, Ebner F, Kreienberg R, et al. Comparing the outcome between multicentric and multifocal breast cancer: what is the impact on survival, and is there a role for guideline-adherent adjuvant therapy? A retrospective Multicenter cohort study of 8,935 patients. Breast Cancer Res Treat. 2013;142:579-90.
15. Ataseven B, Lederer B, Blohmer JU, Denkert C, Gerber B, Heil J, et al. Impact of multifocal and multicentric disease on surgery and locoregional. Distant and overall survival of 6.134 breast cancer patients treated with neoadjuvant chemotherapy. Ann Surg Oncol. 2015;22:1118-27.
16. Patani N, Carpenter R. Surgical and aesthetic considerations of conservational surgery for multifocal/ multicentric breast cancer. Breast J. 2010;16:222-32.
17. Kaplan J, Giron G, Tartter PI, Bleiweiss IJ, Estabrook A, Smith SR. Breast conservation in patients with multiple ipsilateral synchronous cancers. J Am Coll Surg. 2003;197(5):726-9
18. Julious SA. Estimating sample sizes in clinical trail. CRC:2009.
19. Tot T, Gere M, Pekar G, Tarjan M, Hofmeyer S, Hellberg D, et al. Breast cancer multifocality, disease extent, and survival. Hum Pathol. 2011;42(11):1761-9.
20. Chung AP, Huynh K, Kidner T, Mirzadehgan P, Sim MS, Giuliano AE. Comparison of outcomes of breast conserving therapy in multifocal and unifocal invasive breast cancer. J Am Coll Surg. 2012;215(1):137-46.
21. Boyages J, Jayasinghe UW, Coombs N. Multifocal breast cancer and survival: each focus does matter particularly for larger tumours. Eur J Cancer. 2010;46(11):1990-6.
22. Joergensen LE, Gunnarsdottir KA, Lanng C, Moeller S, Rasmussen BB. Multifocality as a prognostic factor in breast cancer patients registered in Danish Breast Cancer Cooperative Group (DBCG) 1996–2001. Breast. 2008;17(6):587-91.
23. Pedersen L, Gunnarsdottir KA, Rasmussen BB, Moeller S, Lanng C. The prognostic influence of multifocality in breast cancer patients. Breast. 2004;13(3):188-93.
24. Vera-Badillo FE, Napoleone M, Ocana A, Templeton AJ, Seruga B, Al-Mubarak M, et al. Effect of multifocality and multicentricity on outcome in early stage breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2014;146(2):235-44.
25. Senkus E, Kyriakides S, Penault-Llorca F, Poortmans P, Thompson A, Zackrisson S, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi7-23.
26. Leopold KA, Recht A, Schnitt SJ, Connolly JL, Rose MA, Silver B, et al. Results of Conservative Surgery and Radiation Therapy for Multiple Synchronous Cancers of One Breast. Int J Radiat Oncol Biol Phys. 1989;16(1):11-6.
27. Lim W, Park EH, Choi SL, Seo JY, Kim HJ, Chang MA, et al. Breast conserving surgery for multifocal breast cancer. Ann Surg. 2009;249:87-90.
28. Gentilini O, Botteri E, Rotmensz N, Da Lima L, Caliskan M, Garcia-Etienne CA, et al. Conservative surgery in patients with multifocal/multicentric breast cancer. Breast Cancer Res Treat. 2009;113:577-83.
29. Kari M Rosenkranz, Karla Ballman, Linda McCall, Charlotte Kubicky, Laurie Cuttino, Huong Le-Petross, et al. The feasibility of breast-conserving surgery for multiple ipsilateral breast cancer: An initial report from ACOSOG Z11102 (Alliance) trial. Ann Surg Oncol. 2018;25:2858-66.

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The effect of a penile fracture on ejaculatory and erectile functions: A cross-sectional study

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Ethics Committee Approval
Istanbul Prof. Dr. Cemil Taşçıoğlu Clinical Research Local Ethics Committee approved the study protocol with decision number 002 on 21/01/2020.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: There is not enough data in the literature about ejaculatory and erectile functions after a penile fracture. We aimed to report the post-fracture ejaculatory and erectile function change and their relationship with the psychological condition of the patient.
Methods: We retrospectively evaluated 27 patients with a penile fracture who were treated surgically. Pre-fracture and post-fracture ejaculatory and erectile functions were evaluated with Intravaginal Ejaculation Latency Time (IELT) and International Index of Erectile Function (IIEF) questionnaires. The psychological conditions of the patients after the fracture were evaluated with the Beck depression score.
Results: The mean IELT was increased after penile fracture (P=0.007). The post-fracture and pre-fracture IIEF scores were similar (P=0.062). There was a positive correlation between Beck depression score and post-fracture IELT (r=0.498; P=0.008).
Conclusions: According to our results, ejaculation time was longer after penile fractures. It may be related to neurogenic damage due to trauma or the post-fracture psychological condition. However, larger studies with long-term outcomes may reveal the relationship more thoroughly.

Keywords: Penile fracture, Ejaculation time, Erectile dysfunction, Depression

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Introduction

Penile fracture is an uncommon urologic emergency that is defined as the rupture of the tunica albuginea surrounding the corpus cavernosum. The incidence of penile fracture is 1/750,000, and patients in the fourth and fifth decades are affected predominantly [1,2]. The main etiologic mechanism of a penile fracture is the traumatic bend of the penis during erection. The most common reason is trauma during sexual intercourse [3]. Other common causes include masturbation and rolling over one's penis during a night erection [4, 5]. The injury may be accompanied by a dorsal neurovascular bundle and partial or complete urethral damage [6]. Conservative treatment has high complication rates [7]. Therefore, the best treatment is an immediate surgical intervention with the closure of the tunica albuginea and evacuation of the hematoma [8].

Complications such as erectile dysfunction, penile deviation, priapism, urethrocavernosal fistula, and urethral stricture may occur despite immediate surgical intervention [9]. Ejaculatory problems were reported after penile fracture in a recent study [10]. Ejaculatory dysfunction may be related to the penile injury or post-traumatic emotional conditions. There is no data about the relationship between ejaculation time and penile fracture in the literature. We aimed to investigate the effects of penile fracture and post-fracture psychological conditions on ejaculatory and erectile functions.

Materials and methods

We retrospectively analyzed the patients with a penile fracture who visited our Urology Outpatient Clinic. After scanning the data between January 2010 and November 2019, we reached a total of 27 patients with available data. Istanbul Prof. Dr. Cemil Taşçıoğlu Clinical Research Local Ethics Committee approved the study protocol with decision number 002 on 21/01/2020. The study was conducted in line with the Declaration of Helsinki. Written detailed informed consent was obtained from all subjects. Patients with available pre-fracture Intravaginal ejaculation latency time (IELT) and International Index of Erectile Function (IIEF) score data were included in the study. The patients with missing or unavailable data were excluded to prevent bias. All patients were operated on within 4-6 hours after the fracture. Sexual intercourse was forbidden for 6 weeks after the fracture to prevent complications. Demographic data, thorough medical and fracture histories of the patients, and sexual positions during intercourse were obtained from patient archive files.

All patients were evaluated for ejaculation time, erectile functions, and psychologic conditions. IIEF was used to evaluate the erectile capacity of the patients [11]. Post-fracture psychological conditions of patients were evaluated with Beck Depression Inventory [12]. We used the IELT to compare pre-fracture and post-fracture ejaculation times [13]. The control visit time of the patients was 3 months after the penile fracture.

Statistical analysis

The data were analyzed with the Statistical Package for Social Sciences (SPSS) version 22.0™ (IBM Corporation). Descriptive statistics, namely, mean, standard deviation, median, frequency, percentages, minimum, and maximum were presented. The distribution of the variables was assessed with the Shapiro-Wilk test. Wilcoxon Signed Ranks test was used to compare quantitative variables before and after the fractures. Spearman's correlation analysis was used to evaluate the relationship between quantitative variables. All *P*-values were two-tailed and a *P*-value of <0.05 was considered statistically significant.

Results

We evaluated 27 penile fracture patients treated surgically between January 2010 and November 2019 in Istanbul Prof. Dr. Cemil Taşçıoğlu City Hospital. General characteristics of all are presented in Table 1. The mean age of patients was 41.22 (9.55) years, and the mean body mass index (BMI) was 26.05 (3.44) kg/m^2. Eight patients smoked. The etiology was sexual intercourse in 16 patients and masturbation in eight. The etiology of the remaining 3 patients was rolling over one's penis during night erection. The penile fracture was bilateral in 9 patients. Urethral injury accompanied penile fracture in 10 patients. We also questioned the sexual intercourse position of the patients during the fracture. The "man on top" position was reported in 7 patients and the "woman on top" position was reported by nine. The mean Beck depression score of patients was 9.07 (2.5) after the penile fracture.

Table 1: General characteristics of penile fracture patients

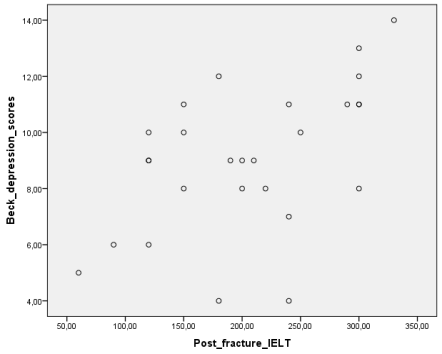
	n:27 mean (SD)
Age	41.22 (9.55)
BMI, kg/m^2	26.05 (3.44)
Cigarette (Yes/No)	8/19
Etiology	
Sexual intercourse	16
Masturbation	8
Rolling over during night erection	3
Sexual position	
Man on top	7
Woman on top	9
BECK depression score	9.07 (2.5)
Accompanying urethral injury	10/27
Bilateral cavernosal injury	9/27

Ejaculatory and erectile features of patients are presented in Table 2. Pre-fracture and post-fracture mean IELTs of the patients were 186.2 (80) sec and 205.55 (75) sec, respectively (*P*=0.007), while the pre-fracture and post-fracture mean IIEF scores were 29.16 (2.94) and 23.96 (6.16), respectively (*P*=0.062). The correlation graph of post-fracture IELT and Beck depression scores is presented in Figure 1. There was a positive correlation between post-fracture IELT and Beck depression scores (r=0.498; *P*=0.008).

Table 2: Ejaculatory and erectile features of patients

	Pre-fracture	Post-fracture	*P*-value
IELT, mean (SD) (secs)	186.2 (80)	205.55 (75)	0.007
IIEF score, mean (SD)	26.19 (2.94)	23.96 (6.16)	0.062

Figure 1: Scatter plot of post-fracture IELT and Beck depression scores; There is a positive correlation between them. (r=0.498; *P*=0.008)



Discussion

Penile fracture is one of the most traumatic injuries of the penis. In the early period of injury, immediate detumescence, severe edema, and hematoma are the most marked symptoms. A penile fracture may cause other long-term complications such as erectile dysfunction, priapism, urethrocavernosal fistula, and urethral stricture. The relationship between erectile function and a penile fracture was investigated in some studies. To the best of our knowledge, there is no study comparing pre-fracture and post-fracture ejaculatory functions.

Increased or decreased penile sensation may develop after penile fracture, due to injury to the accessory structures of the penis. This is also related to the magnitude of trauma. Penile fracture affects human psychology and is one of the frequent reasons for delayed ejaculation. Therefore, the effect of penile fracture and psychological conditions on sexual functioning is a topic worth researching.

Barros et al. reported premature ejaculation and delayed ejaculation cases after penile fracture in their study [10]. However, data on sexual function after an injury is limited. We compared the patients' mean pre- and post-fracture IELTs and found post-fracture IELT to be significantly longer. The dorsal side of tunica albuginea is thicker than the ventral side. Therefore, penile fracture commonly occurs at the ventral tunica albuginea. Ejaculatory functions may be protected in minor penile fractures due to the far localization of the neurovascular bundle from the ventral side. More traumatic injuries may affect the neurovascular bundle and ejaculation times can change. More studies using the traumatic scale can clearly show the relationship.

Sexual activity is important for the quality of men's life and may be affected by penile trauma via psychological factors [14]. Boncher et al. [15] reported that there was a loss of self-confidence leading to anxiety and depression in penile fracture patients and their partners during their early follow-up. This may be related to a fear of recurrence. Similarly, Muentener et al. [16] reported that sexual dysfunction and psychological stress were observed in penile fracture patients. We found a positive correlation between IELT and Beck depression scores. This correlation shows the effect of psychological status on ejaculation time.

Erectile dysfunction is one of the most important complications after a penile fracture. Zargooshi et al. [5] reported that ED rates were very low (1.4%) after surgical treatment and higher (80%) after conservative treatment. There is not still a valid cut-off time for surgery to prevent the complications. However, early surgical intervention and tunica defect repairing are recommended to prevent long-term complications [17-19]. Some studies report that the severity of erectile dysfunction worsens after surgically-treated penile fractures in the long term [20]. On the other hand, studies are showing that erectile functions and sexual potency were preserved in patients treated surgically [21, 22]. In our study, there was not a clear change in IIEF scores after the fracture. There may be confounding factors about the ED etiology. Age and pre-fracture erectile function status have important roles in the future erectile potency of the patient. ED is more likely in elderly patients and erectile functions may worsen in patients who had ED before the fracture. Therefore, the erectile functions of the patients should always be evaluated preoperatively.

In the "woman on top" position, the female partner usually manages the movements. A penile fracture may develop in vigorous action that occurs outside the control of the male partner. Some studies showed that the "woman on top" position has a risk factor for penile fracture [23, 24]. In our study, we found that in 9 of 16 cases, the penile fracture occurred during the "woman on top" position. However, there was not an obvious predominance. The other risk factor may be the BMI of the patients. The mean BMI of the patients with penile fracture was 26.41 (2.06) kg/m^2 in this study. Low-weight people may be more active and faster during sex. Thus, there may be a relationship between male-weight and vigorous action. However, there is insufficient data to define BMI as a risk factor for penile fracture.

Limitations

Our study has some limitations. First, our follow-up time is short, and the study has a small number of patients. Second, detailed neurophysiologic evaluations are needed to demonstrate possible neurogenic injury which may affect ejaculation time. In addition, we did not use a valid scale to evaluate the severity of the penile fracture.

Conclusion

Penile fracture is a very traumatic injury for men, which may lead to complications such as ejaculatory and erectile function failure despite timely surgery. We showed that ejaculation time increases after penile fracture cases. The most probable reason is the post-fracture psychological condition of patients. Further studies with larger numbers of patients may elucidate the factors affecting ejaculation functions. We hope that this study will lead to future work on this subject.

References

1. Koifman L, Barros R, Júnior RA, Cavalcanti AG, Favorito LA. Penile fracture: diagnosis, treatment, and outcomes of 150 patients. Urology. 2010 Dec;76(6):1488-92. doi: 10.1016/j.urology.2010.05.043. Epub 2010 Aug 12. PMID: 20708223.
2. Gelbard MK. Fractured penis: diagnosis and management--a comment. J Sex Med. 2010 Jun;7(6):2288. doi: 10.1111/j.1743-6109.2010.01813.x. Epub 2010 Apr 26. PMID: 20456633.
3. Kamdar C, Mooppan UM, Kim H, Gulmi FA. Penile fracture: preoperative evaluation and surgical technique for optimal patient outcome. BJU Int. 2008 Dec;102(11):1640-4; doi: 10.1111/j.1464-410X.2008.07902.x. Epub 2008 Aug 14. PMID: 18710448.
4. Ateyah A, Mostafa T, Nasser TA, Shaeer O, Hadi AA, Al-Gabbar MA. Penile fracture: surgical repair and late effects on erectile function. J Sex Med. 2008 Jun;5(6):1496-502. doi: 10.1111/j.1743-6109.2007.00769.x. Epub 2008 Feb 4. PMID: 18266649.
5. Zargooshi J. Sexual function and tunica albuginea wound healing following penile fracture: An 18-year follow-up study of 352 patients from Kermanshah, Iran. J Sex Med. 2009 Apr;6(4):1141-1150. doi: 10.1111/j.1743-6109.2008.01117.x. Epub 2008 Dec 4. PMID: 19138357.
6. Haas CA, Brown SL, Spirnak JP. Penile fracture and testicular rupture. World J Urol. 1999 Apr;17(2):101-6. doi: 10.1007/s003450050114. PMID: 10367369.
7. Yapanoglu T, Aksoy Y, Adanur S, Kabadayi B, Ozturk G, Ozbey I. Seventeen years' experience of penile fracture: conservative vs. surgical treatment. J Sex Med. 2009 Jul;6(7):2058-63. doi: 10.1111/j.1743-6109.2009.01296.x. Epub 2009 Apr 28. PMID: 19453898.
8. Penbegul N, Bez Y, Atar M, Bozkurt Y, Sancaktutar AA, Soylemez H et al. Ozen S. No evidence of depression, anxiety, and sexual dysfunction following penile fracture. Int J Impot Res. 2012 Jan-Feb;24(1):26-30. doi: 10.1038/ijir.2011.42. Epub 2011 Sep 15. PMID: 21918532.
9. Eke N. Fracture of the penis. Br J Surg. 2002 May;89(5):555-65. doi: 10.1046/j.1365-2168.2002.02075.x. PMID: 11972544.
10. Barros R, Lacerda G, Schul A, Ornellas P, Koifman L, Favorito LA. Sexual complications of penile fracture in men who have sex with men. Int Braz J Urol. 2018 May-Jun;44(3):550-554. doi: 10.1590/S1677-5538.IBJU.2017.0520. PMID: 29493183; PMCID: PMC5996807.
11. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. Urology. 1999 Aug;54(2):346-51. doi: 10.1016/s0090-4295(99)00099-0. PMID: 10443736.
12. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961 Jun;4:561-71. doi: 10.1001/archpsyc.1961.01710120031004. PMID: 13688369.
13. Serefoglu EC, Cimen HI, Ozdemir AT, Symonds T, Berktas M, Balbay MD. Turkish validation of the premature ejaculation diagnostic tool and its association with intravaginal ejaculatory latency time. Int J Impot Res. 2009 Mar-Apr;21(2):139-44. doi: 10.1038/ijir.2008.58. Epub 2008 Nov 20. PMID: 19020523.
14. Bolat MS, Özen M, Önem K, Açıkgöz A, Asci R. Effects of penile fracture and its surgical treatment on psychosocial and sexual function. Int J Impot Res. 2017 Nov;29(6):244-249. doi: 10.1038/ijir.2017.31. Epub 2017 Oct 19. PMID: 29047457.

15. Boncher NA, Vricella GJ, Jankowski JT, Ponsky LE, Cherullo EE. Penile fracture with associated urethral rupture. Case Rep Med. 2010;2010:791948. doi: 10.1155/2010/791948. Epub 2010 Nov 7. PMID: 21076536; PMCID: PMC2975082.
16. Muentener M, Suter S, Hauri D, Sulser T. Long-term experience with surgical and conservative treatment of penile fracture. J Urol. 2004 Aug;172(2):576-9. doi: 10.1097/01.ju.0000131594.99785.1c. PMID: 15247735.
17. Lee SH, Bak CW, Choi MH, Lee HS, Lee MS, Yoon SJ. Trauma to male genital organs: a 10-year review of 156 patients, including 118 treated by surgery. BJU Int. 2008 Jan;101(2):211-5. doi: 10.1111/j.1464-410X.2007.07265.x. Epub 2007 Oct 8. PMID: 17922859.
18. Tal R, Hall MS, Alex B, Choi J, Mulhall JP. Peyronie's disease in teenagers. J Sex Med. 2012 Jan;9(1):302-8. doi: 10.1111/j.1743-6109.2011.02502.x. Epub 2011 Oct 7. PMID: 21981606.
19. Ralph D, Gonzalez-Cadavid N, Mirone V, Perovic S, Sohn M, Usta M et al. Trauma, gender reassignment, and penile augmentation. J Sex Med. 2010 Apr;7(4 Pt 2):1657-67. doi: 10.1111/j.1743-6109.2010.01781.x. PMID: 20388163.
20. Hatzichristodoulou G, Dorstewitz A, Gschwend JE, Herkommer K, Zantl N. Surgical management of penile fracture and long-term outcome on erectile function and voiding. J Sex Med. 2013 May;10(5):1424-30. doi: 10.1111/jsm.12107. Epub 2013 Feb 27. PMID: 23445526.
21. Nason GJ, McGuire BB, Liddy S, Looney A, Lennon GM, Mulvin DW et al. Sexual function outcomes following fracture of the penis. Can Urol Assoc J. 2013 Jul-Aug;7(7-8):252-7. doi: 10.5489/cuaj.199. PMID: 24032060; PMCID: PMC3758941.
22. Gamal WM, Osman MM, Hammady A, Aldahshoury MZ, Hussein MM, Saleem M. Penile fracture: long-term results of surgical and conservative management. J Trauma. 2011 Aug;71(2):491-3. doi: 10.1097/TA.0b013e3182093113. PMID: 21278611.
23. Reis LO, Cartapatti M, Marmiroli R, de Oliveira Júnior EJ, Saade RD, Fregonesi A. Mechanisms predisposing penile fracture and long-term outcomes on erectile and voiding functions. Adv Urol. 2014;2014:768158. doi: 10.1155/2014/768158. Epub 2014 Apr 13. PMID: 24822062; PMCID: PMC4005103.
24. Tijani KH, Ogo CN, Ojewola RW, Akanmu NO. Increase in fracture of the penis in south-west Nigeria. Arab J Urol. 2012 Dec;10(4):440-4. doi: 10.1016/j.aju.2012.07.004. Epub 2012 Aug 15. PMID: 26558065; PMCID: PMC4442948.

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The clinical importance of triglyceride/glucose ratio in the primary prevention of cardiovascular diseases: A retrospective cohort study

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Çanakkale Onsekiz Mart University clinical research ethics committee (11.11.2020/ 2011-KAEK-27/2020-E.2000141331)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Atherosclerosis plays a significant role in cardiovascular diseases. Dyslipidemia, inflammation, genetics, and environmental factors greatly impact the development and progression of atherosclerosis. This study aimed to investigate the importance of triglyceride-glucose ratio in primary cardiovascular event prevention.

Methods: Our retrospective cohort study included 56 patients (39 males, 17 females). Coronary computed tomography angiography (CCTA) images of the individuals were examined, and calcium score was calculated using the Agatston score. Those with a score of zero and those with scores>0 were included in Groups 1 and 2, respectively. Triglyceride/glucose (TyG) ratio and atherosclerotic cardiovascular disease (ASCVD) risk were calculated for all individuals.

Results: Among all patients, 69.6% had coronary artery calcium scores (CACs) of greater than zero. The TyG ratios were 0.92 (0.33) and 1.77 (0.83) in Groups 1 and 2, respectively (P<0.001). The ASCVD risk was 4.17 (4.92) in Group 1, and 16.24 (10.66) in Group 2 (P<0.001). The TyG ratio was positively correlated with calcium score and ASCVD risk (r=0.717, P<0.001 and r=0.456, P<0.001, respectively). TyG ratio (OR=33.132, 95% CI=4.404-249.254, P=0.001) predicted CACs in CTBA in the univariate logistic analysis. The cut-off level for the TyG ratio in the prediction of coronary atherosclerosis was 1.04, with a sensitivity of 74%, and a specificity of 88% (AUC=0.84, P<0.001).

Conclusion: The present study showed that the TyG ratio could assist the current risk assessment scores used for primary prevention in cardiovascular diseases.

Keywords: Cardiovascular diseases, Coronary calcium score, Prevention

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Introduction

Cardiovascular diseases (CVD) are among the chronic non-communicable diseases, which cause the highest mortality and morbidity in developed countries, despite rapid technological developments and improvements in risk factors in recent years [1]. The high incidence of CVD increased the routine use of noninvasive imaging methods in addition to invasive imaging methods such as coronary artery angiography (CAG) for diagnosis and treatment [2]. Coronary computed tomography angiography (CCTA) provides excellent diagnosis and is the preferred anatomical test for patients with an ASCVD score of 5-7.5 indicating moderate CV risk [3].

CCTA, which is a non-invasive method, has high sensitivity in predicting coronary artery disease (CAD). The coronary artery calcium score (CACs), obtained by performing CBTA, gives valuable information on the prediction and prognosis of patients [4]. Several studies showed that CACs is correlated with the percentage of stenosis in coronary arteries and the plaque burden causing stenosis. When CACs is zero, atherosclerotic activity is very likely to be excluded [5].

Various scoring systems are used in the risk assessment of CVD. Age, hypertension, smoking, and total cholesterol values are used in the current risk scoring systems [6]. Fasting blood glucose and plasma triglyceride levels are not included in most scoring systems; however, certain studies emphasized the importance of including the two values in risk classifications [7].

Triglyceride glucose (TyG) index, which can be calculated logarithmically, is a new marker proven for its relationship with carotid atherosclerosis and insulin resistance [8].

This study aimed to investigate the relationship of TyG ratio to CACs with a simpler calculation, and its usability in primary protection against CVD.

Materials and methods

Study population

This retrospective cohort study examined the coronary computed tomography angiography images obtained between January 2018 and September 2020 of 56 individuals with low and medium risk for coronary artery disease, who presented to the cardiology outpatient clinic. The medical history and laboratory values of the patients, whose calcium scores were calculated through the images, were also examined. The population of the study was divided into two groups as Group 1, including the individuals with CACs values equal to zero, and Group 2, consisting of patients with CACs values greater than zero.

According to the SCORE risk table, patients older than 40 years and younger than 65 years were deemed eligible. Calculation of cardiovascular risk in individuals aged between 40-65 years was made using the SCORE risk table as recommended in the guidelines, and individuals under 40 and over 65 years of age were excluded because the risk table calculates the scores of patients in a certain age range [9]. Cardiovascular risk calculation was performed in patients who presented with chest pain and had a pre-diagnosis of coronary artery disease in the outpatient clinic, and patients with low and medium risk who underwent CCTA examination were included. Patients with chronic renal failure, acute coronary syndrome, active infection, malignant disease, cerebrovascular disease, coronary artery bypass, and stent history, patients who were scheduled for serious valve surgery and prosthetic valves, those with low-density lipoprotein (LDL) cholesterol values over 190 mg/dl, those with lipid metabolism disorders, hypertension or diabetes were not included. No patient was taking cholesterol-lowering medication. According to the CCTA report, less than 50% of all patients had nonsignificant stenosis in their coronary arteries.

Blood samples obtained from the antecubital veins after 12 hours of fasting were analyzed on the Beckman Coulter LH-780 device (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland). The results of complete blood count, lipid panel, and kidney function tests were obtained. Blood samples were studied before CCTA.

The Score risk chart published on the https://www.heartscore.org website was used for the calculation of 10-year fatal CVD risks (ASCVD) [10]. A post-hoc power analysis was performed with G*Power (software version 3.1.9.6). An effect size of 0.75, alpha error of 0.05, and 17 patients in group 1 and 39 patients in group 2 yielded a power of 0.8167938 for the independent samples t-test.

Prior to the study, the approval of the Çanakkale Onsekiz Mart University Clinical Research Committee was obtained (Date: 11.11.2020 and Decision no: 2020-13/2011-KAEK-27/2020-E.2000141331). Our study was conducted in accordance with the Helsinki Declaration.

Calcium score of coronary arteries

Calcium scoring was performed using a 64-slice CT device (Acquilion 64 Toshiba, Japan, and Sensation 64 Siemens, Germany). The imaging was performed per the technique recommended in the literature, and the amount of calcification was calculated with Agatston scoring. An Agatston score of zero indicates that there is no calcification in the atherosclerotic plaque. An increase in the score indicates that the individual is at risk for cardiovascular disease [11].

The triglyceride/glucose (TyG) ratio was obtained by dividing the fasting triglyceride (mg/dl) value by the serum glucose (mg/dl) value.

Statistical analysis

SPSS 21.0 (SPSS Inc, Chicago, IL, USA) software was used for statistical analysis. Whether the variables conformed to the normal distribution was evaluated using the Shapiro-Wilk test. While the mean ± standard deviation was used in the presentation of continuous variables, percentage and number were used for categorical variables and the data were presented as median (minimum-maximum) for non-normally distributed continuous variables. Student's test analysis was performed for the normally distributed parametric values between groups, and the Chi-square test was used to compare the differences between categorical variables. Pearson's correlation analysis was used to determine the relationship between the TyG ratio, calcium score, and ASCVD risk. Univariate logistic regression analysis was performed to determine CACs in CTBA. The ROC curve analysis was performed to determine the accuracy of the ASCVD

risk and TyG ratio values in predicting coronary atherosclerosis. A *P*-value of <0.05 was considered statistically significant.

Results

The basic clinical and laboratory values of the groups are presented in Table 1.

Table 1: Demographic, clinical and laboratory features of the patients

Variables	Group 1(n=17) (CACs =0)	Group 2 (n=39) (CACs >0)	*P*-value
Age (years), mean (SD)	46.2 (6.5)	56.8 (7.4)	<0.001
Female (n, %)	8(47.1)	9(23.1)	0.078
HT (n, %)	0(0)	22(56.4)	<0.001
DM (n, %)	2(11.8)	11(28.2)	0.160
Current smoker (n, %)	7(41.2)	23(59)	0.219
Serum glucose (mg/dL), mean (SD)	100.90 (19.73)	118.45 (34.95)	0.058
Creatinine (mg/dL), mean (SD)	0.76 (0.12)	0.87 (0.20)	0.013
TSH (mU/L), mean (SD)	0.76 (0.38)	0.76 (0.43)	0.992
LDL-C (mg/dL), mean (SD)	111.77 (25.61)	126.16 (39.50)	0.301
Triglyceride (mg/dL), mean (SD)	90.82 (26.41)	200.11 (79.72)	<0.001
HDL-C (mg/dL), mean (SD)	50.04 (11.94)	50.61 (10.82)	0.860
Total cholesterol (mg/dL), mean (SD)	175.52 (14.62)	206.61 (41.64)	0.004
WBC count, (x10^3 µL), mean (SD)	8.33 (1.60)	7.86 (1.93)	0.465
Hemoglobin (g/dL), mean (SD)	13.91 (1.58)	14.33 (1.26)	0.331
TyG ratio, mean (SD)	0.92 (0.33)	1.77 (0.83)	<0.001
ASCVD risk, mean (SD)	4.17 (4.92)	16.24 (10.66)	<0.001

DM: Diabetes mellitus, HT: Hypertension, TSH: Thyroid Stimulating Hormone, LDL-C: Low-density lipoprotein, HDL-C: High-density lipoprotein, WBC: White blood cell, TyG: Triglyceride-glucose, ASCVD: Atherosclerotic cardiovascular disease, CACs: Coronary artery calcium scores

The mean age of all individuals was 56 (8.6) years. Of the 56 individuals, 39 were male and 17 were female. Individuals with a calcium score greater than zero were older than the others. Group 2 had significantly higher total cholesterol and creatine values compared to Group 1 (*P*<0.05 for both parameters). In the group with a calcium score greater than zero, the TyG ratio and the risk of ASCVD were significantly higher (*P*<0.001 for both parameters). In the correlation analysis, the TyG ratio was positively correlated with the ASCVD risk and the calcium score (r=0.456, *P*<0.001 and r=0.717, *P*<0.001, respectively) (Table 2). Ty (*P*=0.027), total cholesterol (*P*=0.039), ASCVD risk (*P*=0.011) and TyG ratio (*P*=0.001) were predictors of CACs in CTBA in the univariate logistic regression (Table 3).

Table 2: Correlation coefficients for TyG

Variable	r	*P*-value
ASCVD risk	0.456	<0.001
CACs	0.717	<0.001

ASCVD: Atherosclerotic cardiovascular disease, TyG: Triglyceride-glucose, CACs: Coronary artery calcium scores

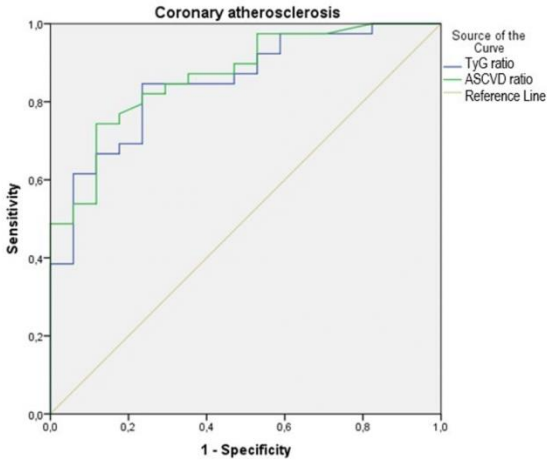
Table 3: Univariate regression analysis to determine CACs in CCTA

Variables	B	OR	*P*-value
Female gender	-1.086	0.338	0.078
HT	21.264	1.716	0.998
DM	1.081	2.946	0.194
Current smoker	0.720	2.054	0.223
LDL-C	0.012	1.012	0.141
Triglyceride	0.015	1.016	0.027
HDL-C	0.005	1.005	0.857
Total cholesterol	0.016	1.016	0.039
ASCVD risk	1.060	2.887	0.011
TyG ratio	3.500	33.132	0.001

SE: Standard error, OR: Odds ratio

The ROC analysis, which was performed to determine the accuracy of the ASCVD risk and TyG ratio values in predicting coronary atherosclerosis, is presented in Figure 1. The area under the curve (AUC) value of the ASCVD risk was 0.86 (95% confidence interval (CI): 0.74-0.95, *P*<0.001), and the AUC value of TyG ratio was 0.84 (95% CI: 0.74-0.95, *P*<0.001).

Figure 1: Receiver operating characteristic (ROC) curves for ASCVD ratio and TyG raito in the prediction of coronary atherosclerosis



Discussion

To the best of our knowledge, this is the first study to reveal the usability of the TyG ratio for primary prevention as well as its relationship with the ASCVD risk and coronary calcium scores of the individuals. Important results were obtained by statistical analysis. First, it was noticed that the TyG ratio could be used to prevent cardiovascular diseases, such as the ASCVD risk. Second, a positive correlation was detected between the coronary calcium score, which provides important insights into the detection of atherosclerotic activity, and the TyG ratio.

Atherosclerosis starts early in life and can cause various clinical pictures in the advanced decades. Pre-identification of CVD and the measures that can be taken by identifying reversible risk factors would reduce the clinical poor outcomes such as stroke and myocardial infarction (MI). Previous studies proved that the coronary calcium burden provides prognostic information in addition to the classic risk factors, and it should be considered when calculating the risk factors [12]. CVD can be excluded when CACs equals zero [13].

In their classification of the atherosclerotic CVD risk, Yader et al. reported that the CACs provided significant information in the long-term prediction of the ASCVD risk [14]. In our study, we demonstrated a significant correlation between ASCVD risk, CACs and TyG ratios. Since this relationship is particularly affected by nutritional habits, individual decisions should be made in clinical use. Triglycerides are fats carried in the blood. Most butter and oils consumed are in the form of triglycerides and the excess calories are converted into triglycerides and stored in fat cells in the body [15].

In their studies on dyslipidemia, Kim and Lee et al. reported that the logarithmically calculated TyG index was associated with arterial stiffness and coronary artery calcification in Korean adults. In another study, the TyG index was an independent predictor of the severity of coronary and peripheral artery diseases. The TyG index was associated with adverse cardiovascular outcomes in the follow-up of diabetes patients with stents diagnosed with acute coronary syndrome [16–18].

In most studies, the TyG index was associated with arterial diseases. We know that the CACs value increases due to the increase in the atherosclerotic activity, and the atherosclerotic activity increases due to the increase in the ASCVD risk [19].

We demonstrated that the TyG ratio, a simpler and practical calculation method, was positively correlated with coronary artery calcification, which is an indicator of atherosclerotic activity. Previous studies reported that dyslipidemia was associated with atherosclerosis, and each cardio-protective condition was had an important role in preventing atherosclerosis [20]. As a result of the correlation and the ROC analysis we performed in our study, we demonstrated that the TyG ratio can be used in primary protection, such as the ASCVD risk, which is associated with the atherosclerotic burden.

Limitation

Its retrospective and single-center design was the main limitation of our study. Another limitation was the small number of individuals included and the lack of follow-up data due to the type of study.

Conclusion

There are various risk factors in the formation of CVD, and it is not possible to include all risk factors in a single scoring system. Considering the literature, although there are various algorithms that can be used to calculate the cardiovascular disease risk of patients, their use in all individuals is limited. Hence, the identification of individual risk factors and their elimination, if possible, are of great importance in primary prevention. Multi-centered prospective studies are needed to elucidate the effects of the TyG ratio on mortality and morbidity in primary prevention, since no long-term follow-up results were available. The ASCVD risk can be obtained from the Score graph recommended in the literature.

References

1. Francula-Zaninovic S, Nola IA. Management of Measurable Variable Cardiovascular Disease' Risk Factors. Curr Cardiol Rev. 2018;14:153-63. PMID: 29473518.
2. Demer LL, Tintut Y. Vascular calcification: pathobiology of a multifaceted disease. Circulation 2008;117:2938–48. PMID: 18519861.
3. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, et al. Implications of Coronary Artery Calcium Testing Among Statin Candidates According to American College of Cardiology/American Heart Association Cholesterol Management Guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2015;66:1657-68. PMID: 26449135.
4. Tota-Maharaj R, Joshi PH, Budoff MJ, Whelton S, Zeb I, Rumberger J, et al. Usefulness of regional distribution of coronary artery calcium to improve the prediction of all-cause mortality. Am J Cardiol. 2015;115:1229-34. PMID: 25743208.
5. Hamilton-Craig CR, Chow CK, Younger JF, Jelinek VM, Chan J, Liew GY. Cardiac Society of Australia and New Zealand position statement executive summary: coronary artery calcium scoring. Med J Aust. 2017;207:357-61. PMID: 29020908.
6. Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: a review for clinicians. Journal of the American College of Cardiology. 2009;54:1209-27. PMID: 19778661.
7. Angoorani P, Heshmat R, Ejtahed HS, Motlagh ME, Ziaodini H, Taheri M, et al. Validity of triglyceride-glucose index as an indicator for metabolic syndrome in children and adolescents: the CACSPIAN-V study. Eat Weight Disord. 2018;23:877-83. PMID: 29453589.
8. Da Silva A, Caldas APS, Hermsdorff HHM, Bersch-Ferreira ÂC, Torreglosa CR, Weber B, et al. Triglyceride-glucose index is associated with symptomatic coronary artery disease in patients in secondary care. Cardiovasc Diabetol. 2019;18:89. PMID: 31296225.
9. Selvarajah S, Kaur G, Haniff J, Cheong KC, Hiong TG, van der Graaf Y, et al. Comparison of the Framingham Risk Score, SCORE and WHO/ISH cardiovascular risk prediction models in an Asian population. Int J Cardiol 2014;176:211–8. PMID: 25070380.
10. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis. 2016;252:207-74.
11. Paixao AR, Berry JD, Neeland IJ, Ayers CR, Rohatgi A, de Lemos JA, et al. Coronary artery calcification and family history of myocardial infarction in the Dallas heart study. JACC Cardiovasc Imaging. 2014;7:679-86. PMID: 24954461.
12. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: A comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000; 20:1262-75. PMID: 10807742.
13. Taylor AJ, Burke AP, O'Malley PG, Farb A, Malcom GT, Smialek J, et al. A comparison of the Framingham risk index, coronary artery calcification, and culprit plaque morphology in sudden cardiac death.Circulation. 2000;101:1243-8. PMID: 10725282.
14. Sandoval Y, Bielinski SJ, Daniels LB, Blaha MJ, Michos ED, DeFilippis AP, et al. Atherosclerotic Cardiovascular Disease Risk Stratification Based on Measurements of Troponin and Coronary Artery Calcium. J Am Coll Cardiol. 2020;76:357-70. PMID: 32703505.
15. Kopčeková J, Holovičová M, Gažarová M, Mrázová J, Habánová M, Mečiarová L, et al. Association between Selected Dietary Habits and Lipid Profiles of Patients with Cardiovascular Disease. Int J Environ Res Public Health. 2020;17:7605. PMID: 33086597
16. Kim MK, Ahn CW, Kang S, Nam JS, Kim KR, Park JS. Relationship between the triglyceride glucose index and coronary artery calcification in Korean adults. Cardiovasc Diabetol. 2017;16:108. PMID: 28830471.
17. Lee SB, Ahn CW, Lee BK, Kang S, Nam JS, You JH, et al. Association between triglyceride glucose index and arterial stiffness in Korean adults. Cardiovasc Diabetol. 2018;17:41. PMID: 29562908.
18. Zhao Q, Zhang TY, Cheng YJ, Ma Y, Xu YK, Yang JQ, et al. Impacts of triglyceride-glucose index on prognosis of patients with type 2 diabetes mellitus and non-ST-segment elevation acute coronary syndrome: results from an observational cohort study in China. Cardiovasc Diabetol. 2020;19:108. PMID: 32641127.
19. Nguyen HL, Liu J, Del CACstillo M, Shah T. Role of Coronary Calcium Score to Identify Candidates for ASCVD Prevention. Curr Atheroscler Rep. 2019;21:53. PMID: 31754800.
20. Martin SS, Blaha MJ, Blankstein R, Agatston A, Rivera JJ, Virani SS, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis. Circulation. 2014;129:77-86. PMID: 24141324.

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Gastroprotective effects of hydrogen sulfide, carbon monoxide and nitric oxide on an experimental ulcer model in rats

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Ethics Committee Approval
The study was approved by the Local Ethical Committee of Eskisehir Osmangazi University (548-1/2017).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Gastric mucosal injury induced by several agents such as ethanol, stress or nonsteroidal anti-inflammatory drugs (NSAIDs) is a common severe disorder. Hydrogen sulfide (H_2S), carbon monoxide (CO) and nitric oxide (NO) are gaseous autacoids that are endogenously produced in mammalian tissues. Recently, several studies confirmed that H_2S, CO and NO play a role in gastroprotection. Our work aimed to evaluate and compared the gastroprotective effects of H_2S, CO and NO on ethanol-, indomethacin- and stress-induced rat ulcer models.
Methods: The effects of NaHS (5 mg/kg), CORM-2 (5 mg/kg) and L-arginine (100 mg/kg) were investigated on gastric ulcer models induced by ethanol (1 ml 96% i.g.), stress (cold+immobility) and indomethacin (40 mg/kg i.g.). The ulcer index, gastric mucus secretion, free and total acidity, and levels of TNF-α, PGE_2, MDA GSH, COX-1, COX-2 were measured.
Results: NaHS and CORM-2 decreased the increased TNF-α and MDA levels in ethanol-induced ulcer. L-arginine reduced mucin secretion, TNF-α and GSH levels in stress-induced gastric ulcer.
Conclusion: The present study showed that H_2S and CO may have gastroprotective activity against ethanol-induced ulcers and NO may be gastroprotective against stress-induced ulcers.

Keywords: Gasotransmitters, Hydrogen sulfide, Carbon monoxide, Nitric oxide, Ulcer

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Introduction

Gastric ulcer is a chronic disorder affecting an increasing number of individuals globally [1]. It develops due to an imbalance between exogenous protective and endogenous aggressive factors such as *Helicobacter pylori*, acid, pepsin, drugs, and mucosal defense mechanisms including mucosal blood flow, mucus production, bicarbonate, prostaglandins, nitric oxide and sulfhydryl compounds [2, 3]. Several different ulcer models are experimentally used for evaluating the gastroprotective activity of potential agents [4]. The animal models of ethanol-induced gastric injury are similar to many aspects of humans and ensure a means for evaluating agents with potential anti-ulcer effects [5]. Oxidative stress, inflammation and reduction of gastric mucus and prostaglandin synthesis are exceedingly involved in ethanol- induced gastric ulcer pathogenesis [6]. Another major etiologic agent of gastrointestinal diseases is the consecutive use of nonsteroidal anti-inflammatory drugs (NSAIDs) which can cause topical injury to the mucosa and systemic effects by inhibiting cyclooxygenase-1 (COX-1), which is associated with mucosal prostaglandin production [7]. Indomethacin, the most popular representative agent among NSAIDs, leads to gastric ulcers by way of generation of reactive oxygen species (ROS), infiltration of leukocytes, inhibition of prostaglandin and induction of apoptosis [8]. The disturbance of gastric mucosal microcirculation, alterations of gastric secretion and abnormal gastric motility might play a role in stress-induced gastric mucosal lesions [9]. Various studies confirmed that stress increased gastric acid secretion [10], decreased prostaglandin synthesis [11] and enhanced lipid peroxidation [12] lead to stress-induced ulcers.

The gaseous mediators, H_2S, CO and NO play a critical role in gastroprotection [13]. Recently several studies indicated that these mediators have gastroprotective effects in different ulcer models [14-16].

This research aimed to assess and compare the possible gastroprotective effects of the three important signaling molecules (H_2S, CO and NO) against different rat ulcer models.

Materials and methods

Animals

Ninety-one Wistar male rats (7-8 weeks old, 250–300 g) were housed in cages in a controlled room with 12/12 light-dark cycles, a temperature of 20-22°C and a relative humidity of 65%-70%. Before the onset of experiments, the animals were kept in a single cage and deprived of food for 16 hours. Free access to water was allowed until 1 hour before the beginning of experiments. This study was performed in compliance with the guidelines for the care and use of laboratory animals approved by the Local Ethics Committee of Eskisehir Osmangazi University (548-1/2017). The rats were divided into thirteen groups (n = 6): (i) Control group (saline, i.p), (ii) Ethanol control group (1 ml 96% i.g.), (iii) Ethanol+L-arginine (100 mg/kg, i.p.) group, (iv) Ethanol+CORM-2 (5 mg/kg, i.g) group, (v) Ethanol+NaHS (5 mg/kg, i.g) group, (vi) Stress group, (vii) Stress+L-arginine (100 mg/kg, i.p.) group, (viii) Stress+ CORM-2 (5 mg/kg, i.g) group, (ix) Stress+NaHS (5 mg/kg, i.g) group, (x) Indomethacin group (40 mg/kg), (xi) Indomethacin+L-arginine (100 mg/kg, i.p.) group, (xii) Indomethacin+CORM-2 (5 mg/kg, i.g) group, (xiii) Indomethacin+NaHS (5 mg/kg, i.g) group.

Drugs

Sodium hydrosulfide (NaHS), L-arginine, tricarbonyldichlororuthenium (II) dimer (CORM-2) and indomethacin were purchased from Sigma-Aldrich (St. Louis, MO, USA). CORM-2 was dissolved in 1% DMSO. The other drugs were dissolved in saline before use. NaHS (5mg/kg, i.g) for H_2S, CORM-2 (5mg/kg, i.g) for CO, and L-arginine (100 mg/kg, i.p.) for NO donor were examined on three gastric ulcer models. These agents were administered orally 1 hour before the induction of ulcers.

Ulcer models

Ethanol-induced gastric ulcer

One ml of absolute ethanol was administered by intragastric gavage. Treatment agents were administered 1 hour before ethanol administration. Two hours after ethanol administration, the rats were sacrificed by decapitation after 3% sevoflurane was given for anesthesia [17].

Stress-induced gastric ulcer

Animals restrained and immobilized in single cages were placed in a ventilated refrigerator at 4 °C for 4 h [18]. Drugs were administered to rats 1 hour before placing them in the refrigerator. After removing them from the refrigerator, the animals were sacrificed as previously described.

Indomethacin-induced ulcer

Gastric ulcer was induced by intragastric gavage of 40 mg/kg of indomethacin. Drugs were given to animals 1 hour before indomethacin administration [19]. Five hours after the administration of indomethacin, they were sacrificed as described previously.

Ulcer index of gastric mucosa

Stomachs of animals were quickly ligated at both ends and removed, and then opened along the great curvature. The ulcerated areas were measured with a magnifying glass. Each lesion (mm) was measured along its greatest length, five petechias were considered to be equivalent to a 1 mm-long ulcer [20]. The ulcer index was recorded and calculated in accordance with the method of Guth [21]. Ulcer length ≤ 1mm (including erosion foci) was scored as 1; 1 mm<ulcer length≤2 mm was scored as 2; 2 mm<ulcer length≤3 mm was scored as 3; 3 mm<ulcer length≤4 mm was scored as 4; ulcer length>4 mm was scored as 5. If ulcer width exceeded 2 mm, the score doubled. The total scores of the whole stomach constituted the ulcer index. After determining ulcer index, each stomach was separated into the corpus and fundus parts.

Corpus was divided into four parts and fundus was divided into six parts, all of which were weighed and stored at -80°C until determination of gastric mucus, TNF-α, PGE_2, MDA GSH, COX-1, and COX-2 levels.

Determination of gastric acidity

For evaluating gastric acidity, the gastric content of the stomachs was collected, washed with 1 ml of saline and centrifuged. Gastric acidity was identified by titration with 0.01 N sodium hydroxide using methyl orange and phenolphthalein for indicators and represented as mEq/L [22].

Determination of gastric mucus

The corpus of the stomach was weighed and used for the determination of gastric mucus content (µg/g tissue) in accordance with the modified procedure of Corne et al. using Alcian blue [23].

Determination of COX-1, COX-2, PGE_2, TNF-α, MDA and GSH

An enzyme-linked immunosorbent assay (ELISA) was performed to measure the level of *COX-1, COX-2, PGE_2, TNF-α, MDA* and *GSH* expression from gastric fundus lysates using the appropriate kits from Shangai YL Biotech, China, per the manufacturer's instructions.

Statistical analysis

SPSS 22 (SPSS Inc, Chicago, IL, USA) software was used for statistical analysis. The results were expressed as mean and the standard error of the mean (SEM). All data were examined for normality of distribution and analyzed by the Kruskal Wallis test followed by Tukey's test. Differences among groups were considered significant if $P<0.05$.

Results

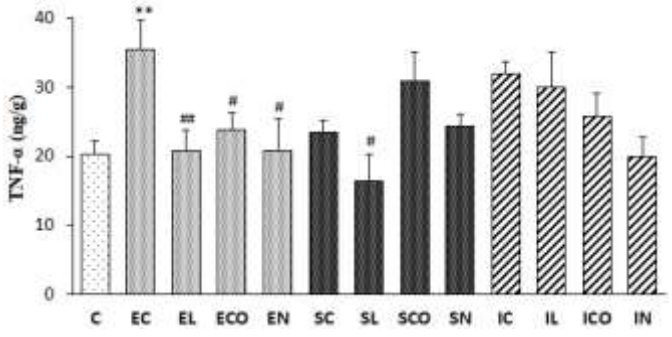
As presented in Table 1, the ulcer index significantly increased in all ulcer models induced by ethanol, stress and indomethacin. Although CORM-2 and NaHS remarkably reduced ulcer index in the ethanol group, no significant change was observed with L-Arginine. L-Arginine caused increased ulceration in the indomethacin group, whereas CORM-2 and NaHS did not change significantly. The levels of mucin presented in Table 1 show that a dramatic increase was noticed in the indomethacin-induced ulcer model with the use of NaHS and mucin secretion was inhibited in the stress group by L-arginine. The effects of all agents on free and total acidity were shown in Table 1. Indomethacin only increased free acidity and L-Arginine reduced it in this group significantly. As shown in Table 1, total acidity was increased by ethanol CORM-2 and NaHS increased total acidity even further, but NaHS decreased total acidity in the stress group. Figure 1 shows that ethanol increased TNF-α levels [35.4 (2.1)], while L-Arginine, CORM-2 and NaHS significantly reduced it in the ethanol group (20.8 (2.9), 23.8 (2.4) and 20.77 (4.7), respectively). On the contrary, they did not significantly change in the indomethacin group. As demonstrated in Figure 2, none of the three agents caused any significant PGE_2 changes in the ethanol and stress groups, while they significantly increased PGE_2 values in indomethacin group. MDA levels, which were increased by ethanol, [244.9 (16.7)] were reduced with NaHS and CORM-2 [133.4 (28.3) and 155.86 (13.9)] (Figure 3). As shown in Figure 4, L-Arginine significantly reduced GSH in the stress group [15.39 (2.0)], whereas the other agents did not cause a remarkable change in other groups. Figure 5 indicates that ethanol increased while L-Arginine and NaHS [1.62 (0.3) and 1.41 (0.4)] decreased COX-1 in the ethanol group, only L-Arginine decreased COX-1 in the stress ulcer group [1.68 (0.4)], and CORM-2 significantly increased COX-1 in the indomethacin group [2.29 (0.2)]. As shown in Figure 6, ethanol increased, while L-Arginine and CORM-2 notably decreased COX-2 in the ethanol group [0.25 (0.07) and 0.33 (0.03)] and increased COX-2 in indomethacin group [0.31 (0.01) and 0.36 (0.04)]. It was also noticed that COX-2 was inhibited by indomethacin.

Table 1: The comparison of ulcer index, mucin, free acidity and total acidity

Treatment	Ulcer Index	Mucin (mg/g tissue)	Free Acidity (meq/L)	Total Acidity (meq/L)
Control	0.132 (0.013)	2.12 (0.43)	0.8 (0.21)	1.36 (0.22)
Ethanol Control	45.1 (1.21)**	3.14 (0.31)	1.67 (0.17)	7.74 (0.46)**
Ethanol+L-Arginine	39.82 (0.73)	2.79 (0.55)	2.23 (0.49)	9.63 (0.64)$^{\#}$
Ethanol+CORM-2	19.67 (1.06)$^{\#\#}$	4.69 (0.34)	1.49 (0.36)	11.4 (0.75)$^{\#\#}$
Ethanol+NaHS	2.57 (0.46)$^{\#\#\#}$	5.63 (0.44)$^{\#\#}$	1.23 (0.46)	12.85 (0.76)$^{\#\#}$
Stress Control	6.5 (0.26)*	5.98 (1.12)**	0.95 (0.37)	2.03 (0.39)
Stress+L-Arginine	2.9 (0.72)	1.19 (0.21)$^{\#\#\#}$	0.56 (0.18)	1.59 (0.40)
Stress+CORM-2	20.9 (0.69)$^{\#\#}$	4.51 (0.2)	0.68 (0.11)	2.74 (0.55)
Stress+NaHS	9.2 (1.16)	3.49 (0.17)$^{\#}$	0.23 (0.05)	1.07 (0.16)$^{\#}$
Indomethacin Control	21.23 (1.14)**	3.34 (0.43)	1.73 (0.19)*	3.14 (0.56)
Indomethacin+L-Arginine	37.1 (0.66)$^{\#\#\#}$	3.14 (0.19)	0.73 (0.16)$^{\#\#}$	3.98 (0.80)
Indomethacin+CORM-2	25.73 (0.49)	7.17 (0.93)	1.89 (0.52)	5.59 (0.64)
Indomethacin+NaHS	24.93 (1.09)	12.14 (0.56)$^{\#\#}$	1.98 (0.34)	6.27 (0.63)$^{\#}$

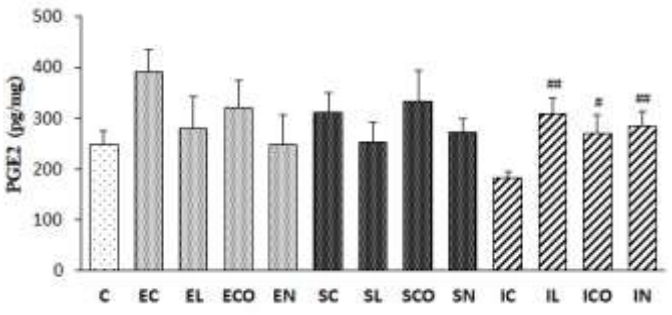
All values are mean (SEM). Compared with control group *; $P<0.05$, **; $P<0.01$. compared with their own control group #; $P<0.05$, ##; $P<0.01$, ###; $P<0.001$. Kruskal-Wallis post hoc Tukey's test.

Figure 1: Effects of H_2S, CO and NO on TNF-α production in the rat gastric tissue of ethanol, stress and indomethacin-induced gastric ulcers.



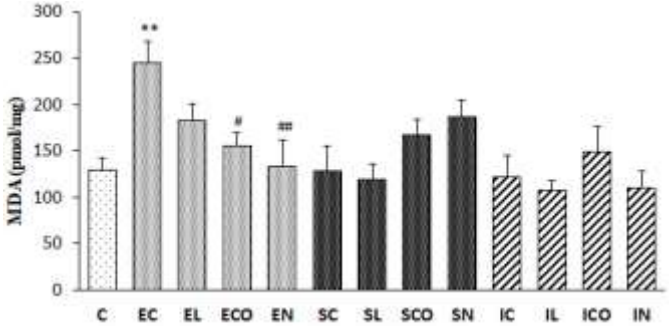
All data represent the mean (SEM) C: Control. EC: Ethanol control. SC: Stress control. IC: Indomethacin control. L: L-arginine. CO: CORM-2. N: NaHS). Significance is represented as **; $P<0.01$ compared to control group and #; $P<0.05$ ##; $P<0.01$ compared to their own control group. Kruskal-Wallis post hoc Tukey's test.

Figure 2: Effects of H_2S, CO and NO on PGE_2 production in the rat gastric tissue of ethanol, stress and indomethacin-induced gastric ulcers.



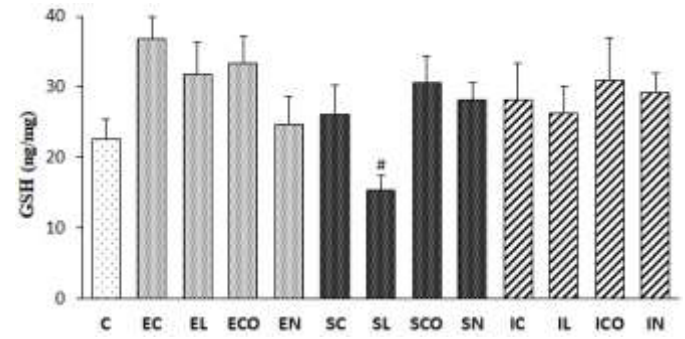
All data represent the mean (SEM), C: Control. EC: Ethanol control. SC: Stress control. IC: Indomethacin control. L: L-arginine. CO: CORM-2. N: NaHS). Significance is represented as #; $P<0.05$, ##; $P<0.01$ compared to their own control group. Kruskal-Wallis post hoc Tukey's test.

Figure 3: Effects of H_2S, CO and NO on MDA production in the rat gastric tissue of ethanol, stress and indomethacin-induced gastric ulcers.



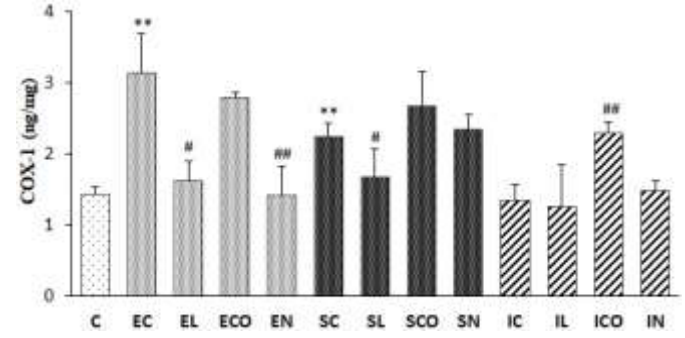
All data represent the mean (SEM), C: Control. EC: Ethanol control. SC: Stress control. IC: Indomethacin control. L: L-arginine. CO: CORM-2. N: NaHS). Significance is represented as **; $P<0.01$ compared to control group and #; $P<0.05$, ##; $P<0.01$ compared to their own control group. Kruskal-Wallis post hoc Tukey's test.

Figure 4: Effects of H_2S, CO and NO on GSH production in the rat gastric tissue of ethanol, stress and indomethacin-induced gastric ulcers.



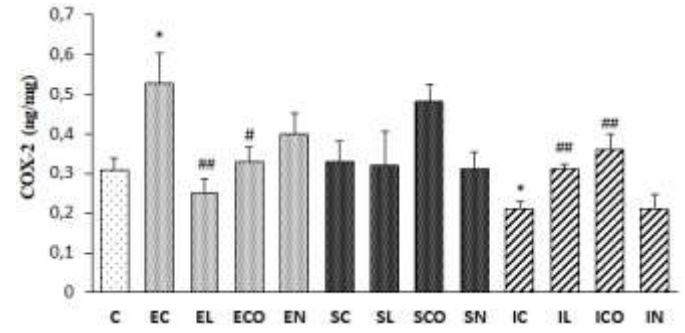
All data represent the mean (SEM, C: Control. EC: Ethanol control. SC: Stress control. IC: Indomethacin control. L: L-arginine. CO: CORM-2. N: NaHS). Significance is represented as $^{\#}$; $P<0.05$ compared to their own control group. Kruskal-Wallis post hoc Tukey's test.

Figure 5: Effects of H_2S, CO and NO on COX-1 levels in the rat gastric tissue of ethanol, stress and indomethacin-induced gastric ulcers.



All data represent the mean (SEM), C: Control. EC: Ethanol control. SC: Stress control. IC: Indomethacin control. L: L-arginine. CO: CORM-2. N: NaHS). Significance is represented as **; $P<0.01$ compared to control group and $^{\#}$; $P<0.05$, $^{\#\#}$; $P<0.01$ compared to their own control group. Kruskal-Wallis post hoc Tukey's test.

Figure 6: Effects of H_2S, CO and NO on COX-2 levels in the rat gastric tissue of ethanol, stress and indomethacin-induced gastric ulcers.



All data represent the mean (SEM), C: Control. EC: Ethanol control. SC: Stress control. IC: Indomethacin control. L: L-arginine. CO: CORM-2. N: NaHS). Significance is represented as *; $P<0.05$ compared to control group and $^{\#}$; $P<0.05$, $^{\#\#}$; $P<0.01$ compared to their own control group. Kruskal-Wallis post hoc Tukey's test.

Discussion

We demonstrated that NaHS and CORM-2 had gastroprotective effects against ethanol-induced ulcers and L-arginine seems to have a protective effect against stress-induced ulcers. However, NaHS, CORM-2 and L-arginine had no gastroprotective effects against indomethacin-induced ulcers. The ulcer inducing mechanisms of ethanol, stress and NSAIDs differ. It is known that ethanol causes activated neutrophil infiltration. Then it leads to an increase in the production of proinflammatory and pro-oxidative enzymes and free radicals, therefore, the gastric mucosa is damaged [24]. Several studies reported that ethanol stimulates pro-inflammatory cytokines which have critical roles in the development of acute gastric ulcers [25]. Ethanol was also shown to reduce the production of NO [26] in the gastric mucosa causing the solubilization of gastric mucus constituents and the development of hemorrhagic lesions [27, 28]. On the other hand it was suggested that high doses of ethanol induce H_2S synthesis in the gastric mucosa, and a decline of H_2S levels to basal conditions protects the gastric tissue [29]. H_2S effects are known to differ by the extent of concentration in the gastric tissue [30]. NSAIDs reduce endogenous gastric H_2S synthesis which protects the gastric mucosa from injury and mediates gastric damage [31]. NaHS prevents ethanol-induced gastric injury in a dose-dependent way [32] and sulfhydryl compounds has gastroprotective activity on ethanol-induced gastric ulcers [33]. An interesting result of our study is that NaHS lead to a significant increase in the nitrite concentration in the indomethacin group. This can be explained by the effect of H_2S on the release of Ca^{2+} via nitric oxide synthase (NOS) activation through the soluble guanylate cyclase (sGC) pathway [34].

Fast restitution and proliferation of gastric cells, maintenance of mucosal blood flow, secretion of protective mucus and bicarbonates, biosynthesis of endogenous prostaglandins (PG), sulfhydryl compounds, endothelial and epithelial nitric oxide (NO) and hydrogen sulfide (H_2S) biosynthesis are among the complex mucosal defense mechanism [35]. PGE_2 was reported to protect the gastric mucosa by an increase in stomach blood flow, and the secretion of mucus and bicarbonate ions ($HCO3^-$) resulting in gastric protection, in part, also mediated by neutralization [36]. It was suggested that PGs synthesized both by COX-1 and COX-2 could participate in the gastroprotective mechanism [37]. In our study, L-arginine inhibited acidity and enhanced COX-1 levels in the stress ulcer group. Even though enhanced levels of mucin were observed by indomethacin, increased acidity and MDA, inhibited COX-2 and PGE_2 led to gastric ulcers dramatically. While CORM-2 and L-arginine stimulated COX-2, NaHS, CORM-2 and L-arginine increased PGE_2 levels and acidity. However, these effects were not enough to protect the indomethacin-induced gastric ulcer, therefore none of these agents had protective activity against this ulcer model.

CO has long been known as a toxic air pollutant. Although it is toxic at elevated concentrations, low concentrations of CO contributed to many physiological effects including anti-inflammatory, anti-apoptotic, anti-proliferative, antioxidant and vasodilatory effects similar to other gaseous mediators such as NO and hydrogen sulfide [38, 39]. The current mechanism of the gastroprotective effect of CO and H_2S has been attributed to an increase in gastric microcirculation and the attenuation of inflammation by downregulation of pro-inflammatory factors in the gastric mucosa [40]. We also had similar results in terms of the effects of CORM-2 and NaHS on TNF-α and COX enzymes, and inhibition of MDA levels in ethanol group. Thus, this local hyperemic activity of H_2S and CO seems to be a basic mechanism of gastroprotection.

NO contributes to the maintenance of gastric mucosal barrier integrity. It also has been reported to increase mucus and bicarbonate secretions, mucosal blood flow, and induce tissue repair when stomach tissue is damaged [41]. Researchers demonstrated that NO plays a biphasic role in the ulcerogenic response of the gastric mucosa and its donors were demonstrated to protect against gastric mucosa damage by several agents [42-44]. We found that NO may have protective effects against stress induced ulcer. In support of our results, some studies have shown

the role of endogenous NO in the protection of gastric mucosa in stress ulcer models [45, 46].

Limitations

The molecular mechanisms of all agents were not clearly investigated to reveal the action in the current study. In addition, species-related alterations can cause significant differences; therefore, future studies should investigate whether the results will be similar when these procedures are performed on different animal species.

Conclusion

H_2S and CO exert anti-ulcerogenic effects and can be effective in reducing the incidence of ethanol-induced gastric mucosal injury. NO may be protective against stress-induced ulcer. These gaseous mediators did not prevent NSAIDs-induced gastric ulcers, even though they stimulated mucin secretion and PGE_2. Our present work may contribute to identify the possible mechanisms underlying their gastroprotective activities.

References

1. Kuna L, Jakab J, Smolic R, Raguz-Lucic N, Vcev A, Smolic M. Peptic Ulcer Disease: A Brief Review of Conventional Therapy and Herbal Treatment Options. J Clin Med. 2019;8(2).
2. Kangwan N, Park JM, Kim EH, Hahm KB. Quality of healing of gastric ulcers: Natural products beyond acid suppression. World J Gastrointest Pathophysiol. 2014;5(1):40-7.
3. Ribeiro AR, do Nascimento Valenca JD, da Silva Santos J, Boeing T, da Silva LM, de Andrade SF, et al. The effects of baicalein on gastric mucosal ulcerations in mice: Protective pathways and anti-secretory mechanisms. Chem Biol Interact. 2016;260:33-41.
4. Adinortey MB AC, Galyuon I, Nyarko A. In Vivo Models Used for Evaluation of Potential Antigastroduodenal Ulcer Agents. Ulcers. 2013;2013:12.
5. Arab HH, Salama SA, Omar HA, Arafa el SA, Maghrabi IA. Diosmin protects against ethanol-induced gastric injury in rats: novel anti-ulcer actions. PLoS One. 2015;10(3):e0122417.
6. Alqasoumi S, Al-Sohaibani M, Al-Howiriny T, Al-Yahya M, Rafatullah S. Rocket "Eruca sativa": a salad herb with potential gastric anti-ulcer activity. World J Gastroenterol. 2009;15(16):1958-65.
7. Matsui H, Shimokawa O, Kaneko T, Nagano Y, Rai K, Hyodo I. The pathophysiology of non-steroidal anti-inflammatory drug (NSAID)-induced mucosal injuries in stomach and small intestine. J Clin Biochem Nutr. 2011;48(2):107-11.
8. Beck PL, Xavier R, Lu N, Nanda NN, Dinauer M, Podolsky DK, et al. Mechanisms of NSAID-induced gastrointestinal injury defined using mutant mice. Gastroenterology. 2000;119(3):699-705.
9. Allen A, Flemstrom G. Gastroduodenal mucus bicarbonate barrier: protection against acid and pepsin. Am J Physiol Cell Physiol. 2005;288(1):C1-19.
10. Levenstein S, Kaplan GA, Smith M. Sociodemographic characteristics, life stressors, and peptic ulcer. A prospective study. J Clin Gastroenterol. 1995;21(3):185-92.
11. Govindarajan R, Vijayakumar M, Singh M, Rao Ch V, Shirwaikar A, Rawat AK, et al. Antiulcer and antimicrobial activity of Anogeissus latifolia. J Ethnopharmacol. 2006;106(1):57-61.
12. Das D, Banerjee RK. Effect of stress on the antioxidant enzymes and gastric ulceration. Mol Cell Biochem. 1993;125(2):115-25.
13. Farrugia G, Szurszewski JH. Carbon monoxide, hydrogen sulfide, and nitric oxide as signaling molecules in the gastrointestinal tract. Gastroenterology. 2014;147(2):303-13.
14. Magierowska K, Magierowski M, Hubalewska-Mazgaj M, Adamski J, Surmiak M, Sliwowski Z, et al. Carbon Monoxide (CO) Released from Tricarbonyldichlororuthenium (II) Dimer (CORM-2) in Gastroprotection against Experimental Ethanol-Induced Gastric Damage. PLoS One. 2015;10(10):e0140493.
15. Mard SA, Neisi N, Solgi G, Hassanpour M, Darbor M, Maleki M. Gastroprotective effect of NaHS against mucosal lesions induced by ischemia-reperfusion injury in rat. Dig Dis Sci. 2012;57(6):1496-503.
16. Brzozowski T, Konturek PC, Drozdowicz D, Konturek SJ, Zayachivska O, Pajdo R, et al. Grapefruit-seed extract attenuates ethanol-and stress-induced gastric lesions via activation of prostaglandin, nitric oxide and sensory nerve pathways. World J Gastroenterol. 2005;11(41):6450-8.
17. Velazquez-Moyado JA, Martinez-Gonzalez A, Linares E, Bye R, Mata R, Navarrete A. Gastroprotective effect of diligustilide isolated from roots of Ligusticum porteri coulter & rose (Apiaceae) on ethanol-induced lesions in rats. J Ethnopharmacol. 2015;174:403-9.
18. Senay EC, Levine RJ. Synergism between cold and restraint for rapid production of stress ulcers in rats. Proc Soc Exp Biol Med. 1967;124(4):1221-3.
19. Kianbakht S MK. Effects of Saffron and its Active Constituents, Crocin and Safranal, on Prevention of Indomethacin Induced Gastric Ulcers in Diabetic and Nondiabetic Rats. J Med Plants. 2009;1(29 And S5):30-8.
20. Yildirim E, Sagiroglu O, Kilic FS, Erol K. Effects of nabumetone and dipyrone on experimentally induced gastric ulcers in rats. Inflammation. 2013;36(2):476-81.
21. Guth PH, Aures D, Paulsen G. Topical aspirin plus HCl gastric lesions in the rat. Cytoprotective effect of prostaglandin, cimetidine, and probanthine. Gastroenterology. 1979;76(1):88-93.
22. Batu OS, Erol K. The effects of some nonsteroidal anti-inflammatory drugs on experimental induced gastric ulcers in rats. Inflammopharmacology. 2007;15(6):260-5.
23. Corne SJ, Morrissey SM, Woods RJ. Proceedings: A method for the quantitative estimation of gastric barrier mucus. J Physiol. 1974;242(2):116P-7P.
24. Chatterjee M, Saluja R, Kanneganti S, Chinta S, Dikshit M. Biochemical and molecular evaluation of neutrophil NOS in spontaneously hypertensive rats. Cell Mol Biol (Noisy-le-grand). 2007;53(1):84-93.
25. Almasaudi SB AA, Al-Hindi RR, El-Shitany NA, Abdel-Dayem UA, Ali SS, Saleh RM, et al. Manuka Honey Exerts Antioxidant and Anti-Inflammatory Activities That Promote Healing of Acetic Acid-Induced Gastric Ulcer in Rats. Evidence-Based Complementary and Alternative Medicine. 2017;2017.
26. Niv Y, Banic M. Gastric barrier function and toxic damage. Dig Dis. 2014;32(3):235-42.
27. Hajrezaie M, Golbabapour S, Hassandarvish P, Gwaram NS, AH AH, Mohd Ali H, et al. Acute toxicity and gastroprotection studies of a new schiff base derived copper (II) complex against ethanol-induced acute gastric lesions in rats. PLoS One. 2012;7(12):e51537.
28. Li Q, Hu X, Xuan Y, Ying J, Fei Y, Rong J, et al. Kaempferol protects ethanol-induced gastric ulcers in mice via pro-inflammatory cytokines and NO. Acta Biochim Biophys Sin (Shanghai). 2018;50(3):246-53.
29. Chavez-Pina AE, Tapia-Alvarez GR, Navarrete A. Inhibition of endogenous hydrogen sulfide synthesis by PAG protects against ethanol-induced gastric damage in the rat. Eur J Pharmacol. 2010;630(1-3):131-6.
30. Liu L, Cui J, Song CJ, Bian JS, Sparatore A, Soldato PD, et al. H(2)S-releasing aspirin protects against aspirin-induced gastric injury via reducing oxidative stress. PLoS One. 2012;7(9):e46301.
31. Vandiver M, Snyder SH. Hydrogen sulfide: a gasotransmitter of clinical relevance. J Mol Med (Berl). 2012;90(3):255-63.
32. Medeiros JV, Bezerra VH, Gomes AS, Barbosa AL, Lima-Junior RC, Soares PM, et al. Hydrogen sulfide prevents ethanol-induced gastric damage in mice: role of ATP-sensitive potassium channels and capsaicin-sensitive primary afferent neurons. J Pharmacol Exp Ther. 2009;330(3):764-70.
33. Vendramini-Costa DB, Monteiro KM, Iwamoto LH, Jorge MP, Tinti SV, Pilli RA, et al. Gastroprotective effects of goniothalamin against ethanol and indomethacin-induced gastric lesions in rats: Role of prostaglandins, nitric oxide and sulfhydryl compounds. Chem Biol Interact. 2014;224:206-12.
34. Moustafa A, Habara Y. Hydrogen sulfide regulates Ca(2+) homeostasis mediated by concomitantly produced nitric oxide via a novel synergistic pathway in exocrine pancreas. Antioxid Redox Signal. 2014;20(5):747-58.
35. Konturek SJ. Mechanisms of gastroprotection. Scand J Gastroenterol Suppl. 1990;174:15-28.
36. Pawlik M, Pajdo R, Kwiecien S, Ptak-Belowska A, Sliwowski Z, Mazurkiewicz-Janik M, et al. Nitric oxide (NO)-releasing aspirin exhibits a potent esophagoprotection in experimental model of acute reflux esophagitis. Role of nitric oxide and proinflammatory cytokines. J Physiol Pharmacol. 2011;62(1):75-86.
37. Czekaj R, Majka J, Ptak-Belowska A, Szlachcic A, Targosz A, Magierowska K, et al. Role of curcumin in protection of gastric mucosa against stress-induced gastric mucosal damage. Involvement of hypoacidity, vasoactive mediators and sensory neuropeptides. J Physiol Pharmacol. 2016;67(2):261-75.
38. Andreadou I, Iliodromitis EK, Rassaf T, Schulz R, Papapetropoulos A, Ferdinandy P. The role of gasotransmitters NO, H2S and CO in myocardial ischaemia/reperfusion injury and cardioprotection by preconditioning, postconditioning and remote conditioning. Br J Pharmacol. 2015;172(6):1587-606.
39. Takagi T, Uchiyama K, Naito Y. The therapeutic potential of carbon monoxide for inflammatory bowel disease. Digestion. 2015;91(1):13-8.
40. Magierowski M, Magierowska K, Szmyd J, Surmiak M, Sliwowski Z, Kwiecien S, et al. Hydrogen Sulfide and Carbon Monoxide Protect Gastric Mucosa Compromised by Mild Stress Against Alendronate Injury. Dig Dis Sci. 2016;61(11):3176-89.
41. Takeuchi K, Ohuchi T, Okabe S. Endogenous nitric oxide in gastric alkaline response in the rat stomach after damage. Gastroenterology. 1994;106(2):367-74.
42. Lopez-Belmonte J, Whittle BJ, Moncada S. The actions of nitric oxide donors in the prevention or induction of injury to the rat gastric mucosa. Br J Pharmacol. 1993;108(1):73-8.
43. Andrews FJ, Malcontenti-Wilson C, O'Brien PE. Protection against gastric ischemia-reperfusion injury by nitric oxide generators. Dig Dis Sci. 1994;39(2):366-73.
44. Ribbons KA, Zhang XJ, Thompson JH, Greenberg SS, Moore WM, Kornmeier CM, et al. Potential role of nitric oxide in a model of chronic colitis in rhesus macaques. Gastroenterology. 1995;108(3):705-11.
45. Wei Q, Korejo NA, Jiang J, Xu M, Zheng K, Mao D, et al. Mitigation of stress from gastric mucosal injuries by mulberry extract may occur via nitric oxide synthase signaling in mice. Tissue Cell. 2018;54:59-64.
46. Park CH, Son HU, Son M, Lee SH. Protective effect of Acer mono Max. sap on water immersion restraint stress-induced gastric ulceration. Exp Ther Med. 2011;2(5):843-8.

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Predictors of poor outcome in mushroom poisoning: A retrospective cohort study

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The study was approved by the ethics committee of Ondokuz Mayis University (Decision no: B.30.2.ODM.0.20.08).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Mushroom poisoning (MP) can result in a wide range of clinical presentations from mild gastrointestinal complaints to hepatic necrosis or acute liver failure (ALF) requiring liver transplantation (LT). Although several predictive parameters were studied, a guideline based on a consensus is still lacking. This study aimed to investigate the parameters associated with LT-free survival in patients admitted to the emergency department with MP.
Methods: This retrospective cohort study was conducted on 420 adult patients admitted to the emergency department with symptoms of MP after ingestion of mushrooms. Patients with viral hepatitis, autoimmune liver disease, acetaminophen or salicylate toxicity, or other chronic liver diseases were excluded. Favorable outcome was defined as LT-free survival while adverse outcome was defined as death or LT. Liver transaminase levels, treatment modalities, and outcomes were analyzed.
Results: The median age of the patients was 46.9 (31-60) years and 59.8% were female. The season with the most MP admissions was autumn (57.6%). The latent periods of 337 (80.3%) patients were between 0-6 hours, and of 83 (19.8%), longer than 6 hours. Among them, 227 (54.0%) patients were treated with gastric lavage, 272 (64.8%), with activated charcoal, 27 (6.4%) with conventional therapy (CT) and 2 (0.5%) with hemodialysis. All 420 patients received supportive therapy (ST). Patients who received CT had higher mean AST and ALT levels than patients who received only decontamination or ST (P<0.001). One hundred and sixty-two (38.6%) patients refused further treatment while under observation. Among patients who received CT+ST, patients with adverse outcomes (liver transplant or death) had higher transaminase levels (AST: P=0.009, and ALT: P=0.008) and higher coagulation parameters (PTT: P=0.016, INR: P=0.009).
Conclusion: The duration of the latent period, AST, ALT, PTT, and INR may be used as predictors of poor outcome.

Keywords: Mushroom poisoning, Emergency department, Amanita Phalloides, Prognosis

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Introduction

Most cases of poisonous mushroom exposures result in mild gastrointestinal complaints, while some can lead to hepatic necrosis or acute liver failure (ALF) requiring liver transplantation (LT) [1]. Amanita phalloides (AP) is responsible for over 90% of deaths from mushroom poisoning. Initial symptoms are similar to gastroenteritis which makes an early diagnosis difficult in patients who do not report the ingestion of mushrooms [2]. The main pathophysiology in AP-associated poisoning is ALF with elevated transaminases and bilirubin.

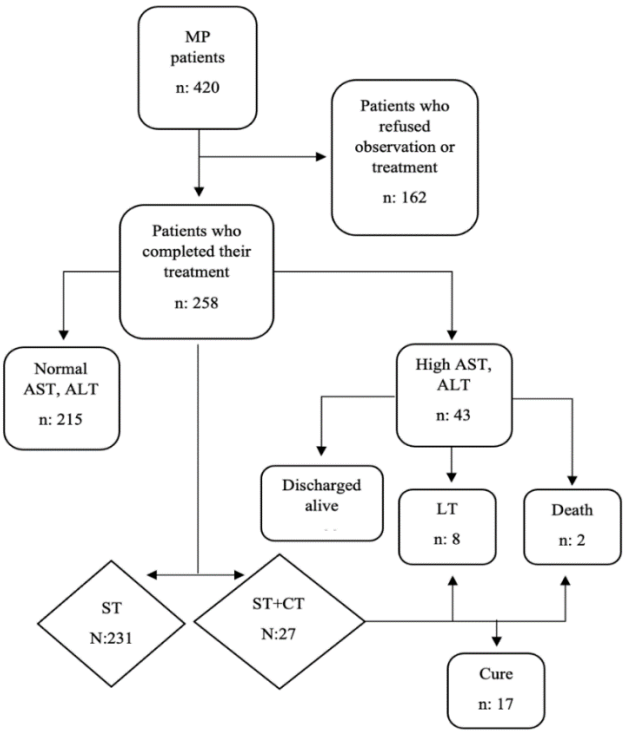
The severity of poisoning depends on the amount of toxin (the lethal dose of α-amanitin for humans is 0.1 mg/kg) and the latent period between ingestion and the initiation of treatment [2, 3]. Several parameters were identified for prognosis; however, none are suggested for deciding the safety of treatment in a local hospital instead of referral to a transplant center [1, 4–6]. An important issue is the lack of a consensus on optimal management despite advancements in the treatment of patients exposed to amatoxin [7]. After oral intake of AP, amatoxins are quickly absorbed in the gastrointestinal system. Therefore, gastric lavage and active charcoal are recommended in the early stages (within 1 hour) of AP ingestion to effectively decrease the absorption of amatoxin [3, 7]. Because of the enterohepatic recirculation of amatoxins, repeated doses of active charcoal are recommended [8]. The therapeutic effects of extracorporeal treatments with hemodialysis, hemoperfusion, or hemofiltration are negligible as the toxins are short-lived in blood plasma [7]. Urgent LT is indicated when decontamination, elimination, or conventional treatments fail to cure the patients. It is critical to make a timely decision for LT as ALF progresses rapidly with only 50-85% of patients surviving until a transplant [9]. The decision to refer to LT may be futile in the presence of multiorgan failure, cerebral edema, or renal failure. Despite several existing criteria for the timing of LT (King's College criteria [10], Escudie's criteria [5], Clichy criteria [11], Ganzert's criteria [12], CLIF-OF [13]), a guideline based on a consensus on this issue is lacking [7, 12].

This study aimed to investigate parameters associated with LT or death free survival in patients admitted to the department (ED) for MP.

Materials and methods

The data of 420 patients aged 18 years or above admitted to the ED with symptoms of poisoning after mushroom ingestion between January 2008 and December 2012 who had laboratory studies (blood count, liver and renal function tests, coagulation parameters) performed were retrospectively analyzed. The diagnosis of MP was made with symptoms following recent ingestion of mushrooms and the exclusion of other diagnoses that could cause similar symptoms or acute liver failure as serum, urine, or stool analysis for fungal toxins cannot be performed in our clinic. Patients with viral hepatitis, autoimmune liver disease, acetaminophen or salicylate toxicity, or other chronic liver diseases were excluded. Age, gender, symptoms at admission, the time between exposure and symptoms (latent period), daily laboratory results, treatments, and outcomes were recorded. Two hundred and fifty-eight (61.4%) patients completed their treatment while 162 (38.6%) refused further treatment while under observation (Figure 1).

Figure 1: Flowchart



The conventional therapy (CT) group consisted of patients with a two-fold or more increase in transaminase levels who received CT. Favorable outcome was defined as LT-free survival while adverse outcome was defined as death or LT. Patients who received an LT after referral were included in the adverse outcome group. Liver transaminase levels, treatment modalities, and outcomes were analyzed. Approval was obtained from the Ondokuz Mayıs University Clinical Studies Ethics Committee (Decision No. B.30.2.ODM.0.20.08). This manuscript is derived from the thesis study "Retrospective analysis of patients admitted to the emergency department with mushroom poisoning."

Statistical analysis

IBM SPSS v23 was used for statistical analysis. Kolmogorov-Smirnov test was used to assess normality. Parameters without normal distribution were compared with the Mann Whitney U test and categorical variables were compared with the Chi-Squared test. Descriptive statistics were presented as median (interquartile range) and frequency (%). Significance was set at $P<0.05$.

Results

This retrospective cohort study was performed on 420 adult patients admitted to the ED between January 2008 – December 2012 after symptoms of poisoning following ingestion of mushrooms. Within the study period, 13.3% (420/3154) of adult poisoning cases were due to mushroom poisoning. There were 251 (59.8%) females, and 169 (40.2%) males, with a median age of 46 (31-40) years. The season with highest number of admissions was autumn (57.6%) and the month with the most admissions was October (31.2%). Two hundred and twenty-seven (80.2%) patients had a latent period of 0-6 hours, while 83 (19.8%) had a latent period of longer than 6 hours. Patient

distribution according to the monthly trend of admissions and the duration of latent period is presented in Table 1.

Table 1: Monthly trend of admissions and durations of latent period

Trend of admission		n (%)
Autumn	September	27 (6.4)
	October	131 (31.2)
	November	84 (20.0)
Total		242 (57.6)
Summer	June	43 (10.2)
	July	58 (13.8)
	August	20 (4.8)
Total		121 (28.8)
Spring	March	7 (1.7)
	April	6 (1.4)
	May	30 (7.1)
Total		43 (10.2)
Winter	December	6 (1.4)
	January	7 (1.7)
	February	1 (0.2)
Total		14 (3.3)
Latent Period	0-6 hours	337 (80.2)
	≥ 6 hours	83 (19.8)

The most frequent complaint at admission was nausea, present in 394 (93.8%) patients, followed by vomiting in 366 (87.1%) patients, and diarrhea in 83 (19.8%) patients. Patients with elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (n=43) had a median latent period of 6 (4-10) hours, while patients with normal AST and ALT levels (n=215) had a median latent period of 2 (1-4) hours (P<0.001). There were 215 (51.2%) patients with normal transaminase levels throughout the treatment and 43 patients (10.2%) with elevated enzymes at admission or during treatment. One hundred and sixty-two (38.7%) refused observation or further treatment. The distribution of patients according to transaminase levels is given in Table 2.

Table 2: The distribution of patients according to transaminase levels

	n (%)	AST (U/L) Median (IQR)	ALT (U/L) Median (IQR)
Normal throughout treatment	215 (51.2)	21.0 (17.8-25.9)	18.0 (13.4 – 24.3)
Normal at admission, high during treatment	9 (2.1)	26.1 (23.4-31.0)	19.8 (14.8 -30.1)
High at admission, Lower during treatment	26 (6.2)	136.0 (61.4-411.3)	142.0 (80.6- 327.9)
Referred for transplant	8 (1.9)	967.7 (322.2-2358.7)	1217.0 (356.3 – 3053.2)
Refused observation or treatment	162 (38.6)	21.3 (17.9-26.8)	18.2 (13.5 -25.1)
Total	420 (100)	21.9 (18.1-28.9)	19.3 (14.1-27.9)

AST: Aspartate aminotransferase (U/L), (Reference range; 8-46), ALT: Alanine Aminotransferase (U/L), (Reference range; 0-35), IQR: Interquartile range

All 258 (61.4%) patients who accepted observation and treatment received repeated doses of activated charcoal along with supportive therapy (ST) (fluids + symptomatic treatment). Twenty-seven (6.4%) patients with a two-fold or more elevation in transaminase levels received CT (treatment with penicillin, silibinin, N-Acetylcysteine (NAC)) along with ST. Patients who received ST+CT had higher transaminase levels than patients who received only ST (P<0.001). Peak laboratory values with different therapies received by the 258 patients who accepted observation and treatment are given in Table 3.

Patients with adverse outcomes (LT + Death) had higher transaminase levels (AST: P= 0.009, ALT: P=0.008), and higher coagulation parameters (PTT: P=0.016, INR: P=0.009) than patients with favorable outcomes (cure). Other laboratory values (T. Bil: P=1.000, D. Bil: P=0.980, BUN: P=0.414, Cre: P=0.407) were not significantly different between the groups (Table 4).

Table 3: Peak laboratory values and patient treatment

	Treatment		
	ST+CT (n=27) Median (IQR)	ST (n=231) Median (IQR)	*P*-value
AST (U/L)	1924.9 655.8-5019.8	21.8 18.3-28.7	<0.001
ALT (U/L)	1987.9 550.0-5148.4	18.3 14.1-26.4	<0.001
T. Bil (mg/dL)	2.0 1.3-4.6	0.6 0.5-1.0	<0.001
D. Bil (mg/dL)	0.6 0.2-2.9	0.1 0.1-0.1	<0.001
BUN (mg/dL)	21.1 15.4-32.3	14.8 11.6-18.6	0.002
Cre (mg/dL)	1.0 0.7-1.6	0.7 0.6-0.9	0.001
PTT (sec)	14.0 11.7- 22.7	11.6 11.0- 12.1	<0.001
INR	1.2 1.1-2.1	1.0 1.0-1.1	<0.001

AST: Aspartate aminotransferase (U/L), ALT: Alanine aminotransferase (U/L), T. Bil: Total Bilirubin (mg/dL), PTZ: Prothrombin Time (sec), INR: International Normalized Ratio, BUN: Blood Urea Nitrogen (mg/dL), Cre: Creatinine (mg/dL), ST: Supportive Treatment, CT: Conventional Treatment, IQR: Interquartile range

Table 4: Peak laboratory values according to outcomes in patients who received conventional therapy

Outcomes in patients who received conventional therapy			
	Cure (n=17) Median (IQR)	LT+Death (n=10) Median (IQR)	*P*-value
AST (U/L)	1147.7 428.4-2315.1	4856.4 1633.6-7993.6	0.009
ALT (U/L)	671.9 436.0-2571.2	4801.6 2244.3-5661.0	0.008
T. Bil (mg/dL)	2.0 1.6-3.2	2.3 1.2-4.7	1.000
D. Bil (mg/dL)	0.6 0.4-2.4	0.4 0.2-3.2	0.980
BUN (mg/dL)	17.2 11.0-33.3	21.2 17.8-30.8	0.414
Cre (mg/dL)	0.9 0.7-1.3	1.2 0.8-2.3	0.407
PTT (sn)	12.3 11.6- 18.0	24.2 13.7- 71.3	0.016
INR	1.1 1.1-1.3	2.2 1.2-7.4	0.009

AST: Aspartate aminotransferase (U/L), ALT: Alanine aminotransferase (U/L), T. Bil: Total Bilirubin (mg/dL), PTT: Prothrombin Time (sec), INR: International Normalized Ratio, BUN: Blood Urea Nitrogen (mg/dL), Cre: Creatinine (mg/dL), LT: Liver Transplantation, IQR: Interquartile range

Of the patients referred for transplant, 8 (1.9%) received an LT. The peak laboratory value of patients referred for LT are given in Table 5. In our clinic, 2 (0.47%) patients aged 78 and 80 years died on the 6th and 8th days of their treatment due to liver failure despite conventional therapy and hemodialysis for acute renal failure. Among 27 patients who received ST + CT due to two-fold or more elevation of transaminases, the death rate was 7.40%.

Table 5: Peak laboratory values of patients referred for liver transplantation

	Reference Range	Median (IQR)
AST (U/L)	8-46	4367 (1541-6657)
ALT (U/L)	0-35	4442 (2110-5429)
T. Bil (mg/dL)	0.1-1.5	1.40 (1.17-3.50)
D. Bil (mg/dL)	0.0-0.4	0.22 (0.20-0.79)
PTT (sec)	10-14	20.75 (13.65-29.35)
INR	0.85-1.15	1.71 (1.24-2.65)
BUN (mg/dL)	5-24	21.98 (17.82-32.21)
Cre (mg/dL)	0.4-1.4	1.08 (0.72-1.40)

AST: Aspartate aminotransferase (U/L), ALT: Alanine aminotransferase (U/L), T. Bil: Total Bilirubin (mg/dL), D. Bil: Direct Bilirubin (mg/dL), PTT: Prothrombin Time (sec), INR: International Normalized Ratio, BUN: Blood Urea Nitrogen (mg/dL), Cre: Creatinine (mg/dL), IQR: Interquartile range

Discussion

The outcomes after mushroom poisoning depend on the type of ingested mushroom, the toxin amount, laboratory values, clinical findings, treatment received, need for hemodialysis, and the need for liver transplantation. Despite a good amount of accumulated knowledge of fungal toxins, there are discrepancies in diagnosis and treatment.

During the study period, 13.3% (420/3154) of adult poisoning cases were due to MP. In a different study from the same region, this rate was 9.3% [14]. In previous reports, MP

was most common in patients aged 35-55 years and women were more frequently affected than men [14–17]. In our study, the median age was 46.9 (31-60) years and 59.8% of the patients were female. The seasons with the highest amount of MP admissions are spring and autumn, which can vary with region and climate [14–17]. In this study, 57.6% of MP admissions were in autumn, and the month with the highest number of admissions was October (32.1%). Mushrooms grow primarily in spring and autumn when they are also most harvested and ingested. This seasonality in mushroom growth explains the trend in hospital admissions. MP seen in other seasons occur after ingestion of dried or frozen mushrooms collected in the spring or autumn [16, 17]. Symptoms depend on the type of ingested mushroom, ranging from mild gastrointestinal symptoms to organ failure and death.

Several classifications were proposed to differentiate MP according to the presentation symptoms. Gastrointestinal symptoms are shared across many MP syndromes [17, 18]. In this study, the chief complaint was nausea in 93.8% of the patients followed by vomiting present in 87.1% of the patients. Other complaints included headache, dizziness, malaise, dry mouth, aphasia, dysarthria, diaphoresis, and hypersalivation, which made up 12.8% of all complaints. Mushrooms with slow-acting toxins (most prominent being A. phalloides) cause cellular damage and symptoms of poisoning become eminent within 6-24 hours of ingestion. In A. phalloides poisoning, symptoms include vomiting of increasing severity, abdominal pain, and diarrhea. Liver enzymes are elevated in liver damage. The prognosis depends on the amount of ingested toxins [5, 16]. In our hospital, toxins could not be identified in MP cases, therefore, it was not possible to identify the ingested species in our patients. Patients with elevated transferase levels (n=43) had a median latent period of 6 (4-10) hours, while patients with normal levels (n=215) had a median latent period of 2 (1-4) hours, similar to previous reports in the literature [4, 7, 8, 12]. Although the type of toxins in MP patients could not be determined, poisoning with a latent period of 6-24 hours is caused by slow acting fungal toxins. Amatoxin is responsible for the majority of MP cases with slow acting toxins where liver enzymes are elevated in the early phase due to liver toxicity [8, 9].

Medical treatment strategies against AP poisoning are all nonspecific. There are no randomized trials on the results of CT in MP, and such trials are indeed difficult due to the low number of cases and the ethical challenges of denying an effective treatment. Drugs most used alone or in combination against MP are penicillin G, N-Acetylcysteine, and silibinin [6–8]. Penicillin G and silibinin act by inhibiting amatoxin uptake by the hepatocytes. NAC has antioxidant and glutathione recycling properties. These drugs can be used alone or in combinations [2, 8].

In the poisoning severity score, cases with mild signs or symptoms and a two-fold or more rise in transaminases are classified as minor poisoning [19]. In this study, 27 (%6.4) patients with at least a two-fold increase in transaminases and signs of poisoning received CT (penicillin, silibinin, NAC) in addition to ST. Among patients who received CT + ST, the worse outcome group had higher transaminase levels and higher coagulation parameters than the favorable outcome group (Table 2). After ST + CT, transaminase levels and coagulation parameters returned to normal in 18 (62.9%) patients, while 8 (29.6%) were referred to LT. Patients with late emerging symptoms of gastrointestinal toxicity, failure to respond to CT+ST, and ALF should be referred to centers that can offer an LT [7]. The critical issue with LT is the timing of its decision, however, a consensus is lacking [9]. Our study shows that transaminase levels and coagulation parameters may be used as prognostic markers. Although studies have reported death rates with MP ranging from 2.3% to 3.8%, MP cases who do not receive LT for ALF due to amatoxin have death rates of 10-30% [16,20]. In this study, the death rate among 27 patients who were given CT + ST was 7.40%.

A limitation of this study is that the mushroom species were not identified with measurement of toxin levels. Other limitations are its retrospective design and the low number of severe poisoning cases.

Conclusion

Duration of the latent period, AST, ALT, PTT, and INR may be used as predictors of adverse outcome. Studies with larger number of cases are necessary to further investigate the predictors of outcome in MP.

References

1. Bonacini M, Shetler K, Yu I, et al. Features of Patients With Severe Hepatitis Due to Mushroom Poisoning and Factors Associated With Outcome. Clinical Gastroenterology and Hepatology. 2017;15:776–9. doi: 10.1016/j.cgh.2016.11.039
2. Wennig R, Eyer F, Schaper A, et al. Mushroom Poisoning. Deutsches Arzteblatt International. 2020;117:701–8. doi: 10.3238/arztebl.2020.0701
3. Jaeger A, Jehl F, Flesch F, et al. Kinetics of amatoxins in human poisoning: therapeutic implications. Journal of toxicology Clinical toxicology. 1993;31:63–80. doi: 10.3109/15563659309000374
4. Trabulus S, Altiparmak MR. Clinical features and outcome of patients with amatoxin-containing mushroom poisoning. Clinical Toxicology. 2011;49:303–10. doi: 10.3109/15563650.2011.565772
5. Escudié L, Francoz C, Vinel JP, et al. Amanita phalloides poisoning: Reassessment of prognostic factors and indications for emergency liver transplantation. Journal of Hepatology. 2007;46:466–73. doi: 10.1016/j.jhep.2006.10.013
6. Kim T, Lee D, Lee JH, et al. Predictors of poor outcomes in patients with wild mushroom-induced acute liver injury. World Journal of Gastroenterology. 2017;23:1262–7. doi: 10.3748/wjg.v23.i7.1262
7. Ye Y, Liu Z. Management of Amanita phalloides poisoning: A literature review and update. Journal of Critical Care. 2018;46:17–22. doi: 10.1016/j.jcrc.2018.03.028
8. Diaz JH. Amatoxin-Containing Mushroom Poisonings: Species, Toxidromes, Treatments, and Outcomes. Wilderness and Environmental Medicine 2018;29:111–8. doi: 10.1016/j.wem.2017.10.002
9. Enjalbert F, Rapior S, Nouguier-Soulé J, et al. Treatment of amatoxin poisoning: 20-year retrospective analysis. Journal of toxicology Clinical toxicology. 2002;40:715–57. doi: 10.1081/clt-120014646
10. Yildiz BD, Abbasoglu O, Saglam A, et al. Urgent liver transplantation for Amanita phalloides poisoning. Pediatric Transplantation. 2008;12:105–8. doi: 10.1111/j.1399-3046.2007.00838.x
11. Ferreira R, Romãozinho JM, Amaro P, et al. Assessment of emergency liver transplantation criteria in acute liver failure due to Amanita phalloides. European Journal of Gastroenterology and Hepatology. 2011;23:1226–32. doi: 10.1097/MEG.0b013e32834c7b8f
12. Ganzert M, Felgenhauer N, Zilker T. Indication of liver transplantation following amatoxin intoxication. Journal of Hepatology. 2005;42:202–9. doi: 10.1016/j.jhep.2004.10.023
13. Ye Y, Liu Z, Zhao M. CLIF-OF >9 predicts poor outcome in patients with Amanita phalloides poisoning. American Journal of Emergency Medicine. 2021;39:96–101. doi: 10.1016/j.ajem.2020.01.027
14. Yardan T, Baydin A, Eden AO, et al. Wild mushroom poisonings in the Middle Black Sea region in Turkey: Analyses of 6 years. Human and Experimental Toxicology. 2010;29:767–71. doi: 10.1177/0960327110361758
15. Keller SA, Klukowska-Rötzler J, Schenk-Jaeger KM, et al. Mushroom poisoning—a 17 year retrospective study at a level I university emergency department in Switzerland. International Journal of Environmental Research and Public Health. 2018;15. doi: 10.3390/ijerph15122855
16. Colak S, Kandis H, Afacan MA, et al. Assessment of patients who presented to the emergency department with mushroom poisoning. Human and Experimental Toxicology 2015;34:725–31. doi: 10.1177/0960327114557902
17. Ahishali E, Boynuegri B, Ozpolat E, et al. Approach to mushroom intoxication and treatment: Can we decrease mortality? Clinics and Research in Hepatology and Gastroenterology 2012;36:139–45. doi: 10.1016/j.clinre.2011.11.004
18. White J, Weinstein SA, de Haro L, et al. Mushroom poisoning: A proposed new clinical classification. Toxicon. 2019;157:53–65. doi: 10.1016/j.toxicon.2018.11.007
19. Persson HE, Sjoberg GK, Haines JA, et al. Poisoning Severity Score. Clinical Toxicology. 1998;6:205–13.
20. Brandenburg WE, Ward KJ. Mushroom poisoning epidemiology in the united states. Mycologia. 2018;110:637–41. doi: 10.1080/00275514.2018.1479561.

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Comparison of the clinical and laboratory characteristics of patients with COVID-19 and community-acquired pneumonia

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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: It is challenging to discriminate between COVID-19 and community-acquired pneumonia due to similar clinical features, albeit of great importance. This study aimed to compare the clinical and laboratory characteristics between patients hospitalized due to COVID-19 pneumonia and those with community-acquired pneumonia (CAP).

Methods: This retrospective cohort study included cases who were hospitalized with the diagnosis of COVID-19 between April and December 2020 and those hospitalized with the diagnosis of CAP during the same months in 2019. Statistical differences were investigated by comparing the clinical and laboratory characteristics of the two groups.

Results: The study included 882 cases, comprising 755 with COVID-19 and 127 with CAP. In the COVID-19 pneumonia group, the mean age was lower, there were more women, the hospitalization period was longer, and the rates of hypertension and diabetes mellitus were higher compared to the CAP group ($P<0.05$). The white blood cell (WBC), urea, creatinine, albumin and platelet values were higher in the CAP group ($P<0.05$). The patients who died due to COVID-19 pneumonia had higher mean age, length of hospital stay, C-reactive protein, WBC, urea and creatinine values and lower albumin and platelet levels ($P<0.05$). The rates of hypertension, stroke history, coronary artery disease, congestive heart failure, diabetes mellitus and chronic kidney disease were higher among the patients that died in the COVID-19 group ($P<0.001$ for all).

Conclusion: COVID-19 and community-acquired pneumonia differed from each other in terms of many clinical and laboratory characteristics.

Keywords: COVID-19, Pneumonia, Mortality, Diagnosis, Pulmonary complication

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Introduction

COVID-19 disease, which quickly spread worldwide, affects many parts of the body, especially the respiratory system, and can result in death [1]. According to the data of the World Health Organization published in April 2021, more than 130 million people have been infected with the disease, and globally, nearly 3 million people died. In the USA, where the highest number of cases is seen, over 30 million people were affected by the disease to date. In Turkey, the virus has been reported in 4 million cases, of which 34,000 have resulted in mortality. The COVID-19 pandemic remains a serious problem threatening the human health worldwide [2]. The COVID-19 disease causes pneumonia by affecting the respiratory system. Although COVID-19 pneumonia and community-acquired pneumonia (CAP) have some clinical similarities, their causative agents and treatments differ. Severe respiratory failure and clinical conditions related to infection are observed in both diseases [3]. SARS-CoV-2, the agent of COVID-19 pneumonia, is highly contagious; therefore, patients with this disease are treated in isolation. In addition, admitting patients with CAP to the isolated area reserved for COVID-19 cases should be totally avoided due to the risk of super-infection. Thus, it is very important to differentiate between COVID-19 pneumonia and CAP for the effective treatment and management of these diseases [4, 5].

The diagnosis of COVID-19 disease is confirmed using the reverse-transcription polymerase chain reaction (RT-PCR) test. However, RT-PCR alone is not sufficient to diagnose COVID-19 pneumonia [6, 7], as additional laboratory tests are valuable in PCR-negative patients and those that cannot undergo radiological imaging. In patients with COVID-19, there may be an increase in C-reactive protein (CRP) and an increase or decrease in white blood cell (WBC) count. It has been suggested that changes in laboratory values are associated with the severity of the disease which can be accompanied by bacterial infections [8, 9].

The number of studies comparing the characteristics of CAP and COVID-19 pneumonia is limited. Our aim in this study was to compare the clinical and laboratory characteristics of patients diagnosed with COVID-19 pneumonia and those with CAP to determine the differences between the two groups.

Materials and methods

Study design and population

The study was conducted retrospectively by screening patient files in a tertiary hospital and initiated after obtaining approval from the clinical research Ethics Committee of the Adıyaman University (no: 2021/03-7 date: 16/03/2021). No informed consent forms were obtained due to its retrospective nature.

The study started in April 2020 considering that the first case of COVID-19 pneumonia in Turkey was reported in March 2020 [2]. The study included patients that presented to the emergency department and were hospitalized with the diagnosis of COVID-19 pneumonia over a nine-month period from April to December 2020. Then, patients that were hospitalized due to CAP over the same period in 2019 were identified. Age, gender, length of hospital stay, clinical outcome (mortality and recovery), comorbidities [chronic obstructive pulmonary disease (COPD), hypertension, stroke history, coronary artery disease (CAD), congestive heart failure (CHF), diabetes mellitus (DM), chronic kidney disease (CKD), and malignancy history, laboratory data, including WBC, CRP, platelet, albumin, urea and creatinine values were obtained from the hospital archive and recorded in a form prepared by the researchers. The patients were evaluated in two groups, as those with COVID-19 pneumonia and CAP. The differences were investigated by statistically comparing the characteristics of the patients. In addition, the patients in the COVID-19 pneumonia group were further divided into two subgroups as those that died (mortality) and those that recovered (recovery). The clinical and laboratory characteristics of these patients, which had been recorded previously, were examined to explore factors affecting mortality.

Outpatients were not included in the study. COVID-19 pneumonia group included patients whose diagnoses were confirmed by a PCR test only. The scientific committee suggests hospitalization for patients with COVID-19 based on the presence of one or more of the following criteria: Fingertip oxygen saturation <92%, CRP >10 mg/dL, D-dimer >1,000 ng/ml, and bilateral diffuse involvement (>50%) in radiological imaging. These are the basic hospitalization criteria included in the COVID-19 guidelines, which are constantly updated with additions and omissions when necessary [10]. Our study included patients hospitalized based on any one or more of these criteria. The CAP group included all patients hospitalized with a diagnosis of CAP between April to December 2019, and microbiological agents were not investigated.

To avoid selection bias, the patients were recruited consecutively. Additionally, the diagnoses of all patients were already standardized and definitively determined by quantitative criteria. All patients with specified diagnoses (ICD-10 codes: U07.3, J15, J17.0, J18.0, J18.1, J18.8, J18.9) within the specified period were included in the study. The data collection and analysis were performed by different persons.

Statistical analysis

SPSS software program was used for data analysis (Version 17). Kolmogorov-Smirnov test was used to assess the suitability of continuous data to normal distribution. Student's t-test was used to assess normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. Qualitative data were compared by the Chi-square test. Normally distributed numerical data were shown as mean (standard deviation), and non-normally distributed data were presented as median (min-max). Categorical variables were expressed as numbers and percentages. $P<0.05$ was considered statistically significant.

Results

A total of 882 cases comprising 755 with COVID-19 pneumonia and 127 with CAP were included in the study over a nine-month period. The mean age of all patients was 68.8 (15.9) years, 64.5% were over 65 years. While 26.6% of all patients died at the hospital, the rest were discharged with recovery. Hypertension, chronic arterial disease, DM, and COPD were the most common comorbidities (Table 1).

The mortality rate was 12.6% in the CAP group and 29% in the COVID-19 pneumonia group (P<0.001). The median age was 72 years in the COVID-19 group and 75 years in the CAP group (P=0.04). The ratio of females was higher (P=0.07) and the length of hospital stay was longer (P<0.001) in the COVID-19 group. The CRP level did not significantly differ between the two groups (P=0.113) while WBC, urea, creatinine, and platelet levels were significantly higher in the CAP group (P<0.001). The median albumin value was 3.2 in patients with COVID-19 pneumonia and 3.3 in those with CAP, indicating a statistically significant difference (P=0.049) (Table 1).

While the rate of COPD history was 52% among the patients in the CAP group, it was significantly lower (25%) in the COVID-19 pneumonia group (P<0.001). Stroke history was higher in the patients with CAP (P<0.001). Hypertension was present in 374 patients in the COVID-19 pneumonia group and 48 patients in the CAP group (P=0.014). Similarly, the rate of DM history was significantly higher among patients with COVID-19 (P=0.06). There was no significant difference between the two groups in terms of the rates of CAD, CHF, CKD, and malignancy history (Table 1).

Table 1: Comparison of the baseline characteristics, laboratory findings and comorbidities of the patients

Variables	All n=882	COVID-19 n=755	CAP n=127	*P*-value
Age	68.8 (16)	68.4 (15.5)	71.2 (18)	0.04
Female gender	396 (44.9%)	353 (46.8%)	43 (33.9%)	0.07
Died	235 (26.6%)	219 (29%)	16 (12.6%)	<0.001
Length of hospital stay	8 (1-68)	8 (1-68)	6 (1-38)	<0.001
Laboratory findings				
CRP (mg/dL)	8.1 (0.1-44.7)	7.9 (0.2-28.4)	9.2 (0.1-44.7)	0.113
WBC($\times10^9$/L)	8.4 (1.5-49)	8 (2.7-23.7)	12.6 (1.5-49)	<0.001
Albumin (g/dL)	3.2 (1.2-4.9)	3.2 (1.2-4.4)	3.3 (1.7-4.9)	0.049
Urea (mg/dL)	39 (11-280)	38 (13-128)	51 (11-280)	<0.001
Creatinine (mg/dL)	0.9 (0.4-8.7)	0.9 (0.5-8.7)	1.1 (0.4-3.8)	<0.001
Platelet ($\times10^9$/L)	202 (2-697)	196 (2-697)	246 (48-635)	<0.001
Comorbidities				
Chronic obstructive pulmonary disease	255 (28.9%)	189 (25%)	66 (52%)	<0.001
Hypertension	422 (47.8%)	374 (49.5%)	48 (37.8%)	0.014
Stroke history	121 (13.7%)	89 (11.8%)	32 (25.2%)	<0.001
Malignancy history	73 (8.3%)	60 (7.9%)	13 (10.2%)	0.386
Coronary artery disease	293 (33.2%)	254 (33.6%)	39 (30.7%)	0.516
Congestive heart failure	91 (10.3%)	72 (9.5%)	19 (15%)	0.063
Diabetes mellitus	281 (31.9%)	254 (33.6%)	27 (21.3%)	0.006
Chronic kidney disease	83 (9.4%)	71 (9.4%)	12 (9.4%)	0.987

CAP: community-acquired pneumonia, CRP: C-reactive protein, WBC: while blood cell

Among patients with COVID-19 pneumonia, age, length of hospital stays, and CRP, WBC, urea and creatinine levels were higher while the albumin and platelet levels were lower in the mortality subgroup (P<0.05). In addition, the mortality subgroup of COVID-19 pneumonia had higher rates of hypertension, stroke history, CAD, CHF, DM and CRF compared to the recovery subgroup (P<0.001) (Table 2).

Table 2: Characteristics of the patients with COVID-19 pneumonia according to patient outcome

Variables	Died (n=219)	Recovery (n=536)	*P*-value
Age	76 (40-92)	66 (23-104)	<0.001
Female gender	96 (43.8%)	257 (47.9%)	0.304
Length of hospital stay	10 (1-45)	8 (1-68)	0.002
Laboratory findings			
CRP (mg/dL)	9.5 (0.6-28.4)	7.5 (0.2-23.5)	<0.001
WBC($\times10^9$/L)	8.4(2.9-22.1)	7.6 (2.7-23.7)	0.003
Albumin (g/dL)	3 (1.2-4.4)	3.3 (1.4-4.4)	<0.001
Urea (mg/dL)	48 (19-125)	35 (13-128)	<0.001
Creatinine (mg/dL)	1.1 (0.5-8.7)	0.85 (0.5-7.4)	<0.001
Platelet ($\times10^9$/L)	186 (35-697)	201(2-688)	0.007
Comorbidities			
Chronic obstructive pulmonary disease	63 (28.8%)	126 (23.5%)	0.13
Hypertension	156 (71.2%)	218(40.7%)	<0.001
Stroke history	57 (26%)	32(6%)	<0.001
Malignancy history	21 (9.6%)	39 (7.3%)	0.286
Coronary artery disease	114 (52.1%)	140(26.1%)	<0.001
Congestive heart failure	51 (23.3%)	21(3.9%)	<0.001
Diabetes mellitus	99 (45.2%)	155(28.9%)	<0.001
Chronic kidney disease	42 (19.2%)	29 (5.4%)	<0.001

CRP: C-reactive protein, WBC: white blood cell

Discussion

The COVID-19 disease, which continues to spread unabated across the world, has highly infectious properties that can affect all parts of the body, especially the respiratory system [11]. There are not many studies in the literature on the differentiation of COVID-19 pneumonia and CAP [12, 13]. In the current study, in which we compared the clinical characteristics of COVID-19 pneumonia and CAP, we determined the mortality rate as 29% in the former, which was lower compared to the latter. Richardson et al. [14] reported that the mortality rate of patients hospitalized due to COVID-19 was 21%. In another study, Ciceri et al. [15] determined the mortality rate as 34% in COVID-19 pneumonia. In patients with CAP, the mortality rate is lower [16]. In contrast, there is also research showing no statistically significant difference in mortality rates between COVID-19 pneumonia and CAP [17]. Our results clearly revealed that COVID-19 pneumonia was more mortal, but we consider that the reason for the high mortality rates in both groups is that all patients had the severe form of pneumonia that required hospitalization.

There are not many studies comparing laboratory tests between CAP and COVID-19 pneumonia. Han et al. [18] found normal WBC values in 97% of the patients with COVID-19 pneumonia and high CRP levels in 99%. Zhou et al. [19] found no significant difference in albumin, urea, creatinine, and platelet counts between the two groups, while the patients with CAP were shown to have higher WBC and CRP counts. Tian et al. [17] reported that the patients with COVID-19 had lower WBC and CRP values compared to those with CAP. Similarly, Lin et al. [20] found that the WBC and CRP values were lower in the COVID-19 group compared to the CAP cases. This is in agreement with our finding indicating a higher increase in the number of WBC among the patients with CAP. However, in our study, no difference was observed in the CRP levels between the groups. In addition, unlike the study conducted by Zhou et al., we determined that the urea and creatinine levels and platelet counts were higher in the CAP group and the albumin level was lower in the COVID-19 pneumonia group. The high levels of urea and creatinine in CAP may be due to the use of CURB-65 criteria, which is based on urea and creatinine levels to determine hospitalization indication in this disease.

In a study conducted by Du et al. [21], a history of cerebrovascular disease and that of cardiovascular disease were emphasized as predictors of mortality and hospitalization in COVID-19 pneumonia. Zhou et al. [19] determined that the diseases accompanying COVID-19 pneumonia were mostly hypertension, CAD and DM in hospitalized patients while the rates of COPD and malignancy were higher in CAP. In contrast, they did not detect any difference between COVID-19 and CAP in terms of concomitant chronic diseases. Similarly, Lin et al. [20] found no difference in the comorbidities of the two types of pneumonia. In our study, while hypertension and DM were more common in the COVID-19 group, stroke history and COPD were more frequent among those with CAP.

In studies examining the relationship between COVID-19 pneumonia and mortality, the mortality rate is higher in COVID-19 pneumonia cases with comorbidities [22-24]. The rates of a history of HT, DM, CAD and CRF were significantly higher in the group that did not survive among the patients with COVID-19. In the same study, the WBC, urea and creatinine values were higher, and the albumin and platelet levels were lower in the mortality group [25]. Similarly, in our study, we observed that the rates of HT, stroke history, CAD, CHF, CRF and DM were higher in the mortality subgroup of COVID-19 pneumonia. In addition, age, length of hospital stays, and the WBC, CRP, urea and creatinine values were higher in the mortality subgroup compared to the recovery subgroup.

Limitations

The main limitation of this study concerns its retrospective and single-center design. In addition, all cases hospitalized with a diagnosis of pneumonia in 2019 were considered to be community-acquired without investigating of the possibility of a viral origin. All patients within the specified period were included in the study retrospectively. Therefore, an equality between the genders could not be ensured.

Conclusion

COVID-19 pneumonia has higher rates of mortality, female gender, hypertension and DM, and longer hospitalization period than CAP. Many laboratory values and the presence of comorbidities affected mortality among the patients with COVID-19 pneumonia. These results reveal that the mortality rate is high in patients with COVID-19 pneumonia, especially among those with more comorbidities; therefore, a detailed evaluation and close follow-up is required in this patient group.

References

1. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents. 2020;55(5):105955. doi: 10.1016/j.ijantimicag.2020.105955.
2. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/
3. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45-e67. doi: 10.1164/rccm.201908-1581ST.
4. Olson G, Davis AM. Diagnosis and Treatment of Adults With Community-Acquired Pneumonia. JAMA. 2020;323(9):885-6. doi: 10.1001/jama.2019.21118.
5. Cellina M, Orsi M, Bombaci F, Sala M, Marino P, Oliva G. Favorable changes of CT findings in a patient with COVID-19 pneumonia after treatment with tocilizumab. Diagn Interv Imaging. 2020;101(5):323-4. doi: 10.1016/j.diii.2020.03.010.
6. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 2020;296(2):E32-E40. doi: 10.1148/radiol.2020200642.
7. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. Radiology. 2020;296(2):E115-E117. doi: 10.1148/radiol.2020200432.
8. Zhang W. Imaging changes in severe COVID-19 pneumonia. Intensive Care Med. 2020;46:583–5. doi: 10.1007/s00134-020-05976-w
9. Cao W. Clinical features and laboratory inspection of novel coronavirus pneumonia (COVID-19) in Xiangyang, Hubei. MedRxiv (2020). doi: 10.1101/2020.02.23.20026963
10. https://covid19.saglik.gov.tr/TR-66301/covid-19-rehberi.html
11. Umakanthan S, Sahu P, Ranade AV, Bukelo MM, Rao JS, et al. Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19). Postgrad Med J. 2020;96(1142):753-8. doi: 10.1136/postgradmedj-2020-138234.
12. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. doi: 10.1001/jama.2020.1585.
13. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42. doi: 10.1001/jama.2020.2648.
14. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323(20):2052-9. doi: 10.1001/jama.2020.6775.
15. Ciceri F, Castagna A, Rovere-Querini P, De Cobelli F, Ruggeri A, Galli L, et al. Early predictors of clinical outcomes of COVID-19 outbreak in Milan, Italy. Clin Immunol. 2020;217:108509. doi: 10.1016/j.clim.2020.108509.
16. Lanks CW, Musani AI, Hsia DW. Community-acquired Pneumonia and Hospital-acquired Pneumonia. Med Clin North Am. 2019;103(3):487-501. doi: 10.1016/j.mcna.2018.12.008..
17. Tian J, Xu Q, Liu S, Mao L, Wang M, Hou X. Comparison of clinical characteristics between coronavirus disease 2019 pneumonia and community-acquired pneumonia. Curr Med Res Opin. 2020;36(11):1747-52. doi: 10.1080/03007995.2020.1830050.
18. Han R, Huang L, Jiang H, Dong J, Peng H, Zhang D. Early Clinical and CT Manifestations of Coronavirus Disease 2019 (COVID-19) Pneumonia. AJR Am J Roentgenol. 2020;215(2):338-43. doi: 10.2214/AJR.20.22961.
19. Zhou Y, Guo S, He Y, Zuo Q, Liu D, Xiao M, Fan J, Li X. COVID-19 Is Distinct From SARS-CoV-2-Negative Community-Acquired Pneumonia. Front Cell Infect Microbiol. 2020;10:322. doi: 10.3389/fcimb.2020.00322.
20. Lin YH, Luo W, Wu DH, Lu F, Hu SX, Yao XY, et al. Comparison of clinical, laboratory, and radiological characteristics between SARS-CoV-2 infection and community-acquired pneumonia caused by influenza virus: A cross-sectional retrospective study. Medicine (Baltimore). 2020;99(44):e23064. doi: 10.1097/MD.0000000000023064.
21. Yang HJ, Zhang YM, Yang M, Huang X. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2. Eur Respir J. 2020;56(3):2002439. doi: 10.1183/13993003.02439-2020.
22. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020:e3319. doi:10.1002/dmrr.3319.
23. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Res Care. 2020;8(1):e001343. doi: 10.1136/bmjdrc-2020-001343.
24. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. doi: 10.1056/NEJMoa2002032.
25. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. doi: 10.1016/S0140-6736(20)30566-3.

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The relationship between atherogenic index and coronary collateral circulation

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Ethics Committee Approval
Faculty of Medicine Namık Kemal University Clinical Research Ethics Board, Date: 27.08.2020, Number: 2020.180.07.13
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: The atherogenic index of plasma (AIP) is a simple and useful biomarker that can predict plasma atherogenicity and coronary artery disease (CAD). Previous studies showed a relationship between AIP with CAD. Therefore, we researched the relationship between the AIP and coronary collateral circulation (CCC) in patients with chronic coronary total occlusion (CTO).
Methods: Three hundred and twenty patients who underwent coronary angiography with the diagnosis of stable or unstable angina pectoris between 2015 and 2019 and who had CTO in at least one coronary artery were included in this retrospective study. The AIP was calculated as the logarithm of [Triglyceride (mg/dL) / high-density lipoprotein cholesterol (mg/dL)]. CCC was graded per the Rentrop grading system in patients with CTO after coronary angiography. Rentrop grades were as follows: 0-1: Low-grade (Group 1) CCC, 2-3: High-grade CCC (Group 2).
Results: There were 170 and 150 patients in Groups 1 and 2, respectively, with the mean ages of 63.5 (9.5) years and 61.1 (10.1) years. Mean body mass index, left ventricular ejection fraction, the rate of hypertension, and smoking were similar between the two groups. The rate of diabetes mellitus (DM) was higher in Group 1 (P=0.006). Multivariate analysis showed that AIP (OR: 4.357, CI 95%: 2.741-6.335, P<0.001) and DM (OR: 0.893, CI 95%: 0.826-0.966, P=0.015) were independent predictors of poor CCC.
Conclusion: In our study, we found that a high AIP is related to poor coronary collateral circulation.

Keywords: Cholesterol, Coronary arteries, Atherosclerosis, Collateral circulation

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Introduction

Cardiovascular diseases are among the most important causes of mortality and morbidity. Chronic coronary total occlusion (CTO) is the almost complete obstruction of a coronary artery for more than three months. Major adverse cardiovascular events are observed more frequently in CTO patients. CTO is detected in approximately 20% of patients during coronary angiography [1]. Despite new techniques and devices, recanalization of CTO is difficult and complication rates are high during the procedure. The procedure is unsuccessful in almost 20-35% of patients with CTO [2].

When a coronary artery is completely occluded, collateral vessels progressively dilate and begin to transport blood to the ischemic or infarcted area. The presence of coronary collateral circulation (CCC) is important to avoid damage to the ventricle during infarction. The mechanism of CCC varies in each patient, and vascular growth factors, various mediators, and immune system cells are involved [3]. Improved collateral circulation is important in terms of long-term adverse cardiovascular events.

As known, dyslipidemia is one of the prominent risk factors responsible for the pathogenesis of atherosclerosis in coronary artery disease (CAD). Although low-density lipoprotein cholesterol (LDL-C) is blamed in ischemic heart diseases, there are also new markers to show the presence of CAD. The atherogenic index of plasma (AIP) can be a simple, valuable marker for predicting the severity of CAD and the grade of CCC. The AIP is the logarithm of the TG to HDL-C ratio. Previous studies reported AIP to have a high sensitivity in predicting acute coronary events [4]. Also, it was shown that AIP is a powerful and independent predictor of cardiovascular diseases [5, 6].

The relationship between CCC and AIP in patients with CTO has not been studied. This study aimed to research the relationship between the AIP and CCC.

Materials and methods

Study population

The patients who visited the emergency department of our hospital with the complaint of chest pain and underwent angiography with the diagnosis of acute coronary syndrome (ACS) between June 2015 and November 2019 were included in this retrospective study. Consecutive 350 patients diagnosed with CTO during the angiography procedure were divided into two groups per the Rentrop classification. Rentrop grades were defined as low-grade CCC (0-1) and high-grade CCC (2-3). The total occlusion of the coronary artery with thrombolysis in myocardial infarction (TIMI) grade 0 flow for more than three months was considered CTO. These findings were obtained by examining the patient's history and previous angiography reports. The study was carried out per the Helsinki declaration and approval was obtained from the Ethics Committee of Tekirdag Namık Kemal University Hospital (Date: 27.08.2020, Number: 2020.180.07.13).

Patients with severe liver or renal insufficiency (serum creatinine>2mg/dl), elevated triglyceride levels (≥400mg/dl), active infection, and malignancy, and those taking triglyceride-lowering medications were excluded from the study. After exclusion criteria were implemented, 320 consecutive patients with ACS were included. Data about the patients' basic clinical characteristics (age, sex, medical history, body mass index, smoking status, etc.) were obtained by examining the hospital database.

Fasting blood samples were obtained from all patients 12 hours before the procedure and analyzed by an automated biochemical analyzer. Blood pressure was measured three times using an automatic blood pressure (BP) monitor, with the arm placed at the heart level after a 10-minute rest period, and an average of three measurements was obtained. Patients with an average of these three measurements >140/90 mmHg or those under antihypertensive medication were considered hypertensive. Diabetes mellitus was determined by a fasting plasma glucose level of ≥ 7.0 mmol/L (126 mg/dL), or a glycated hemoglobin A1c of ≥ 6,5%. Those using antidiabetic drugs were also considered to have DM. Hyperlipidemia was determined as being on lipid-lowering therapy or having a total cholesterol level above 220 mg/dl. Dyslipidemia was defined as having LDL-C≥160 mg/dL or total cholesterol≥220 mg/dl or HDL-C<40 mg/dl or TG≥200 mg/dl or a history of taking lipid-lowering therapy. The AIP was calculated by the logarithmic transformation of the ratio of TG and HDL-C concentrations: $\log_{10}$ [TG (mg/dl)/HDL-C (mg/dl)].

Coronary angiography

Coronary Angiography was performed using a standard Judkins' technique through the right femoral artery in standard projections, after informed consent was obtained from each patient by an experienced team of cardiologists. Two independent cardiologists were blinded to the groups when interpreting the coronary angiograms of the patients. CCC was assessed per the Rentrop classification as mentioned in previous studies [3], and the patients were divided into two groups accordingly: Group 1 (Grade 0 and 1) and Group 2 (Grade 2 and 3).

Statistical analysis

SPSS 22.0 statistical software (SPSS Inc, Chicago, IL) program was used for statistical analysis. Continuous variables were reported as mean (standard deviation) for normally distributed data or median (minimum-maximum) for non-normally distributed data. Categorical variables were expressed as percentage and compared with the Chi-square or the Fischer's exact test. The conformation of the data to normal distribution was evaluated with the Kolmogorov-Smirnov test. Two groups were compared with an independent-samples t-test for normally distributed continuous data. Non-normally distributed data were compared with the Mann-Whitney U test. Receiver-operating characteristic analyses (ROC) were used to obtain the cut-off values of AIP for CCC prediction. Multivariate logistic regression analysis was used to identify the independent predictors of poor CCC. A *P*-value of <0.05 was considered statistically significant.

Results

Table 1 shows the baseline characteristics and the laboratory results of the patients. In Group 1, there were 170 patients with a mean age of 63.5 (9.5) years and in Group 2, there were 150 patients with a mean age of 61.1 (10.1) years.

The mean body mass index, left ventricular ejection fraction, age, the rate of hypertension, and smoking were similar between the two groups. The rate of diabetic patients was higher in Group 1 (P=0.006). There was no difference between the two groups in terms of medical treatment. The vessels with chronic total occlusion, and the number of vessels with CAD were similar in both groups. Laboratory parameters of the two groups were similar except for triglyceride, AIP, and lipid parameters. Triglyceride, LDL-C, AIP, and total cholesterol were higher, while HDL-C levels were lower in Group 1 (P<0.001 for all values) (Table 1).

Table 1: Baseline characteristics and laboratory parameters of the patients

Variables	Group 1 (n=170)	Group 2 (n=150)	Total (n=320)	*P*-value
Age (years)	63.5 (9.5)	61.1 (10,1)	62.2 (9.6)	0.941†
Male, n (%)	110(83.3%)	152(80.9%)	262(81.9%)	0.578#
Female, n (%)	22(16.7%)	36(19.1%)	58(18.1%)	0.572#
Hypertension, n (%)	67(50.8%)	109(58%)	176(55%)	0.208#
Smokers, n (%)	83(62.9%)	103(54.8%)	186(58.1%)	0.147#
Diabetes mellitus, n (%)	65(49.2%)	64(34%)	129(40.3%)	0.006#
Body mass index (kg/m^2)	27.9 (3.9)	27.9 (4.4)	27.9 (4.58)	0.984†
Ejection fraction %	45.8 (11.5)	49.9 (12)	49.77 (10.5)	0.052†
Vessel with chronic total occlusion				
LAD, n (%)	89(67.4%)	131(69.7%)	220(68.8%)	0.880#
Cx, n (%)	37(28%)	50(26.6%)	87(27.2%)	0.880#
RCA, n (%)	6(4.5%)	7(3.7%)	13(4.1%)	0.880#
Medical Treatment				
Beta blocker, n (%)	87(65.9%)	108(57.4%)	195(60.9%)	0.128#
Ca–channel blocker, n (%)	12(9.1%)	19(10.1%)	31(9.7%)	0.764#
ACE-I, n (%)	66(50%)	100(53.2%)	166(51.9%)	0.571#
Diuretic, n (%)	13(9.8%)	25(13.3%)	38(11.9%)	0.349#
Acetyl salicylic acid, n (%)	89(67.4%)	116(61.7%)	205(64.1%)	0.291#
Clopidogrel, n (%)	13(9.8%)	15(8%)	28(8.8%)	0.561#
Oral antidiabetic %	34(25.8%)	40(21.3%)	74(23.1%)	0.345#
Insulin%	27(20.5%)	36(19.1%)	63(19.7%)	0.776#
Statin %	83(62.9%)	117(62.2%)	200(62.5%)	0.902#
Number of vessels with coronary artery disease				
One vessel	29(21.9%)	33(17.6%)	62(19.4%)	0.672#
Two vessel	87(65.9%)	132(70.2%)	219(68.4%)	0.672#
Three vessel	17(12.9%)	22(11.7%)	39(12.2%)	0.672#
Laboratory parameters				
Hemoglobin(g/dl)	13.8 (1.23)	13.7 (1.36)	13.5 (1.43)	0.593†
BUN(mg/dl)	18.21(11-46)	15.41(6-40)	17.44(6-46)	0.407*
Creatinine (mg/dl)	1(0.75-1.7)	0.9(0.3-1.7)	0.9(0.3-1.7)	0.421*
Total cholesterol (mg/dl)	248.2 (33.3)	205 (41.1)	213.27 (46.8)	<0.001†
HDL-C (mg/dl)	32(21-50)	48(26-71)	43.65(18-83)	<0.001*
LDL-C (mg/dl)	171.29 (28.9)	128.25 (38.9)	133.8 (43.8)	<0.001†
Triglyceride(mg/dl)	182.35 (75.3)	111.14 (21.9)	145.48 (67.3)	<0.001†
WBC (×10^3/µL)	7.88 (2.31)	8.34 (2.19)	8.04 (2.23)	0.365†
Neutrophil (×10^3/µL)	4.81 (1.64)	5.03 (2.09)	4.8 (1.89)	0.596†
Lymphocyte(×10^3/µL)	2.21 (0.92)	2.24 (0.86)	2.17 (0.89)	0.992†
Monocyte (×10^3/µL)	0.54(0.3-1.44)	0.59(0.28-2)	0.57(0.27-2)	0.383*
MPV, fl	8.37 (1.13)	8.04 (1.15)	8.20 (1.13)	0.056†
Platelet (×10^3/µL)	279.4 (81.6)	279.8 (62.1)	276.7 (69.4)	0.963†
GFR, ml/dk/1.73 m^2	82.03 (14.9)	84.46 (17.03)	81.83 (17.16)	0.928†
AIP	0.74 (1.17)	0.35 (0.11)	0.5 (0.24)	<0.001†

ACE-I; Angiotensin-converting enzyme inhibitors, LAD; Left anterior descending coronary artery, Cx; Circumflex coronary artery, RCA; Right coronary artery, BUN: Blood urea nitrogen, HDL-C: High density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein cholesterol, WBC: White blood cell count, MPV: Mean platelet volume, GFR: Glomerular filtration rate, AIP: Atherogenic index of plasma. #Chi- square test (percentage), *Mann Whitney U (median, minimum-maximum), † Student's t-test (mean (standard deviation))

Logistic regression analysis was executed to predict poor CCC predictors (Table 2). In univariate analysis, total cholesterol (OR [odds ratio]: 0.978, 95% CI [confidence interval]: 0.972-0.985, P<0.001), LDL-C (OR: 0.954, 95% CI: 0.871-0.985, P<0.001), triglyceride (OR: 3.712, 95% CI: 2.429-4.396, P<0.001), low HDL-C (OR: 0.875, 95% CI: 0.673-0.947, P<0.001) AIP (OR: 5.641, 95% CI: 3.556-6.748, P<0.001) and DM (OR: 0.535, 95% CI: 0.338-0.839, P=0.007) were found to be significantly correlated with poor CCC. Multivariate analysis revealed that AIP (OR: 4.357, CI 95%: 2.741-6.335, P<0.001) and DM (OR: 0.893, CI 95%: 0.826-0.966, P=0.015) were independent predictors for poor CCC.

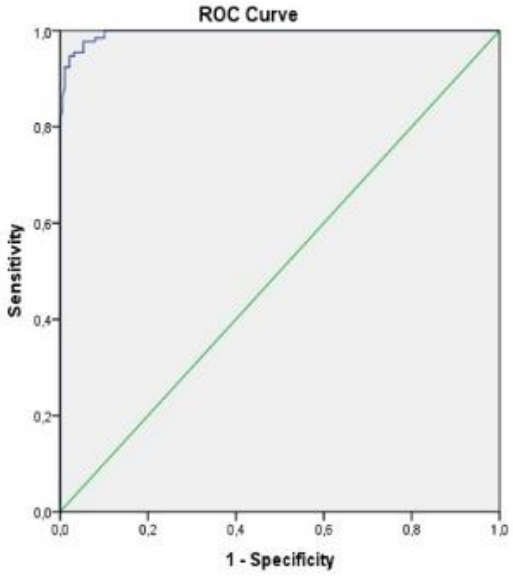
The result of the ROC analysis for the AIP to predict a low degree of coronary collateral circulation was as follows: Cut-off: ≥0.51, AUC: 0.995 and 95% CI: 0.991-0.999 with 95.5% sensitivity and 93% specificity (Figure 1).

Table 2: Univariate and multivariate logistic regression analysis of variables related to poor coronary collateral circulation

Variables	Univariate analysis Odd ratio (95% Confidence interval)	*P*-value	Multivariate analysis Odd ratio (95% Confidence interval)	*P*-value
Total cholesterol (mg/dl)	0.978(0.972-0.985)	<0.001	0.968(0.880-1.065)	0.532
LDL-C (mg/dl)	0.954 (0.871-0.985)	<0.001	1.033(0.944-1.131)	0.454
Triglyceride(mg/dl)	3.712 (2.429- 4.396)	<0.001	---	---
HDL-C (mg/dl)	0.875 (0.673-0.947)	<0.001	---	---
AIP	5.641 (3.556-6.748)	<0.001	4.357 (2.741-6.325)	<0.001
Ejection fraction, %	1.389 (0.681- 1.454)	0.058	--	--
Diabetes mellitus, n	0.535 (0.338-0.839)	0.007	0.893 (0.826-0.966)	0.015
Smoking, n	0.715 (0.454-1.128)	0.149	---	---

LDL: Low-density lipoprotein cholesterol, HDL: High density lipoprotein-cholesterol, AIP: Atherogenic index of plasma

Figure 1: ROC (Receiver operation characteristic) curve and AUC (Area under the curve) for atherogenic index for predicting low coronary collateral circulation grade. (Cut off: 0.51, AUC: 0.995, 95% CI: 0.991- 0.999, P<0.001, 95.5% sensitivity and 93% specificity)



Discussion

Dyslipidemia is the classic risk factor for cardiovascular disease. High triglyceride levels cause both atherogenesis and thrombogenesis. The lipolytic products of triglycerides, which are involved in the pathogenesis of atherosclerosis, activate many proinflammatory, procoagulant, and proapoptotic signaling pathways. AIP is an indirect indicator of small particulate LDL-C. Atherogenic dyslipidemia is defined as a rise in blood TG and LDL-C levels and a decline in HDL-C levels. In previous studies, AIP was associated with LDL-C, HDL-C, and very-low-density lipoprotein (VLDL) particle size [7].

We examined the relationship between the CCC and AIP in patients with ACS who underwent coronary angiography procedures. AIP, as defined by Dobiášová and Frohlich, is an important marker in predicting cardiovascular diseases. Recent CTO studies have reported that AIP correlates with the J-CTO scoring system in predicting the complexity of the lesion [8]. Wan et al. demonstrated that a high AIP is an independent predictor of all-cause mortality in their study [9]. In a prospective cohort including more than 1,000 patients with terminal renal failure, Lee et al. reported the prognostic value of AIP [10]. In various studies, a positive correlation was observed between AIP and diabetes mellitus, arterial stiffness, carotid intima-media thickness [11]. It has also been stated in various studies that AIP can be used in risk assessment before percutaneous coronary intervention (PCI) and coronary artery

bypass grafting (CABG) [12]. In another study, it was demonstrated that AIP could predict restenosis after PCI or CABG [13].

Although many indexes can be used to predict CAD, Lemieux et al. reported that AIP is superior to other indexes such as total cholesterol/HDL-C ratio and LDL-C/HDL-C ratio in CAD estimation [14]. A large Chinese cohort study with over 430 patients showed that increased AIP was independently related to CAD in Chinese males [15]. In a previous study that enrolled 1437 patients without CAD and 2253 patients with CAD, a positive correlation was found between the AIP and SYNTAX score [16]. In another prospective study in which the patients were followed for 4.2 years, a linear relationship was found between AIP and coronary artery calcification progression [15]. In a different study involving 1131 patients newly diagnosed with CAD, AIP was associated with the GRACE score, which predicts major cardiac adverse events [17]. The relationship between AIP and atherosclerosis has been shown in previous studies. We also showed a relationship between AIP and CTO in this study.

Impaired ischemia-induced angiogenesis is the cause of frequent diabetic vascular complications. Angiogenesis is the formation of a new vascular network from the existing main vessels to re-oxygenate the ischemic region. The main underlying cause of diabetic vascular complications is impaired angiogenesis due to ischemia [18]. DM was shown as an independent predictor of poor CCC in a recent study by Chen et al., which included 128 CTO patients [19]. In our study, DM was also an independent predictor of poor CCC.

The most important limitation of our study is that it was conducted with a small group of patients in a single center. In addition, the present study is retrospective, all of which reduce its power. Findings may not be inclusive for other demographic groups. The AIP was calculated only once at admission. Calculating the changes in the AIP during the follow-up period may be better in predicting the prognosis. Further large-scale and multi-center prospective studies are required to validate our results.

Conclusion

In summary, we found that high AIP levels are related to poor collateral circulation in patients with CTO. A high AIP is an important predictor of a low CCC grade. AIP may be a useful marker for prognosis in patients with ACS who underwent percutaneous coronary intervention. It can guide in patient selection for an intervention in CTO.

References

1. Råmunddal T, Hoebers LP, Henriques JP, Dworeck C, Angerås O, Odenstedt J, et al. Chronic total occlusions in Sweden--a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). PLoS One. 2014;9(8):e103850.
2. Stojkovic S, Juricic S, Dobric M, Nedeljkovic MA, Vukcevic V, Orlic D, et al. Improved Propensity-Score Matched Long-Term Clinical Outcomes in Patients with Successful Percutaneous Coronary Interventions of Coronary Chronic Total Occlusion. Int Heart J. 2018 Jul 31;59(4):719-26.
3. Hakimzadeh N, Verberne HJ, Siebes M, Piek JJ. The future of collateral artery research. Curr Cardiol Rev. 2014 Feb;10(1):73-86.
4. Ma X, Sun Y, Cheng Y, Shen H, Gao F, Qi J, Yet al. Prognostic impact of the atherogenic index of plasma in type 2 diabetes mellitus patients with acute coronary syndrome undergoing percutaneous coronary intervention. Lipids Health Dis. 2020 Nov 16;19(1):240.
5. Cai G, Shi G, Xue S, Lu W. The atherogenic index of plasma is a strong and independent predictor for coronary artery disease in the Chinese Han population. Medicine (Baltimore). 2017;96(37):e8058.
6. Mesut E, Cihan A, Orhan G. Is it possible to predict the complexity of peripheral artery disease with atherogenic index? Vascular. 2020;28(5):513-9.
7. Hernández-Reyes A, Vidal Á, Moreno-Ortega A, Cámara-Martos F, Moreno-Rojas R. Waist Circumference as a Preventive Tool of Atherogenic Dyslipidemia and Obesity-Associated Cardiovascular Risk in Young Adults Males: A Cross-Sectional Pilot Study. Diagnostics (Basel). 2020 Dec 2;10(12):1033.
8. Guelker JE, Bufe A, Blockhaus C, Kroeger K, Rock T, Akin I, Behnes M, Mashayekhi K. The atherogenic index of plasma and its impact on recanalization of chronic total occlusion. Cardiol J. 2020;27(6):756-61.
9. Wan K, Zhao J, Huang H, Zhang Q, Chen X, Zeng Z, et al. The association between triglyceride/high-density lipoprotein cholesterol ratio and all-cause mortality in acute coronary syndrome after coronary revascularization. PLoS One. 2015 Apr 16;10(4):e0123521.
10. Lee MJ, Park JT, Han SH, Kim YL, Kim YS, Yang CW, et al. The atherogenic index of plasma and the risk of mortality in incident dialysis patients: Results from a nationwide prospective cohort in Korea. PLoS One. 2017 May 26;12(5):e0177499.
11. Shimizu Y, Nakazato M, Sekita T, Kadota K, Yamasaki H, Takamura N, et al. Association of arterial stiffness and diabetes with triglycerides-to-HDL cholesterol ratio for Japanese men: the Nagasaki Islands Study. Atherosclerosis. 2013;228(2):491-5.
12. Gritzenko O, Chumakova G, Veselovskaya N. Atherogenic indexes as predictors of stenotic complication after percutaneous coronary interventions or coronary artery bypass graft. Atherosclerosis. 2015;241(1):e212.
13. Yildiz G, Duman A, Aydin H, Yilmaz A, Hür E, Mağden K, et al. Evaluation of association between atherogenic index of plasma and intima-media thickness of the carotid artery for subclinic atherosclerosis in patients on maintenance hemodialysis. Hemodial Int. 2013;17(3):397-405.
14. Ni W, Zhou Z, Liu T, Wang H, Deng J, Liu X, et al. Gender-and lesion number-dependent difference in "atherogenic index of plasma" in Chinese people with coronary heart disease. Sci Rep. 2017 Oct 16;7(1):13207.
15. Wang L, Chen F, Xiaoqi C, Yujun C, Zijie L. Atherogenic Index of Plasma Is an Independent Risk Factor for Coronary Artery Disease and a Higher SYNTAX Score. Angiology. 2021 Feb;72(2):181-6.
16. Nam JS, Kim MK, Nam JY, Park K, Kang S, Ahn CW, et al. Association between atherogenic index of plasma and coronary artery calcification progression in Korean adults. Lipids Health Dis. 2020 Jul 2;19(1):157.
17. Liu T, Liu J, Wu Z, Lv Y, Li W. Predictive value of the atherogenic index of plasma for chronic total occlusion before coronary angiography. Clin Cardiol. 2021 Apr;44(4):518-25.
18. Kartono T, Mallapasi MN, Mulawardi MM, Laidding SR, Aminyoto M, Prihantono P. Correlation of HDL cholesterol serum and Wagner's severity level of diabetic foot ulcers. Int J Res Med Sci 2017;5:5129-34.
19. Chen X, Lin Y, Tian L, Wang Z. Correlation between ischemia-modified albumin level and coronary collateral circulation. BMC Cardiovasc Disord. 2020 Jul 8;20(1):326.

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The link between serum ACKR2 level and Crohn's Disease and its activity

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Ethics Committee Approval
The study was approved by the Noninvasive Clinical Research Ethics Committee of Kanuni Sultan Suleyman Training and Research Hospital (Decision number: KAEK/2020.06.96, Dated: 06.2020).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Atypical chemokine receptor (ACKR) family suppresses chemokine response and keeps the inflammatory state under control. This study investigated ACKR2 serum levels, which are thought to have an effect on the extreme inflammatory state in Crohn's disease (CD).
Methods: Active and newly diagnosed Crohn's patients under treatment and a healthy control group were included in this prospective case-control study. Patients under the age of 18 years and those with Crohn's disease in remission were excluded. Clinical, demographic, laboratory parameters and serum ACKR2 levels of the patients were examined. Disease activity was evaluated using the simplified endoscopic score for Crohn's disease (SES-CD) and Crohn's disease activity index (CDAI) index. The relationship between disease activity and serum ACKR2 was evaluated using the Spearman correlation analysis.
Results: A total of 119 subjects (66 CD patients and 53 healthy controls) were included in the study. Serum ACKR2 level was significantly lower in the CD group (4.80 ng/mL) compared to the control group (11.15 ng/mL) (P<0.001). In the correlation analysis between ACKR2 level and disease activity indicators, there was a weak positive correlation with SES-CD and CDAI (r = 0.350 P=0.004, r = 0.252, P=0.041, respectively).
Conclusion: Our data show that the ACKR2 level in active CD is quite low compared to the control group. Despite the increase in disease activity, it is not upregulated at a sufficient level and may have adverse effects on the progression of the disease.

Keywords: ACKR2, Chemokine, Crohn's disease, Inflammation

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Introduction

Chemokines are cytokines which interact with target cells by binding to the receptors of the G protein family, which extend transmembranously [1]. Cytokines are the major regulators of the inflammatory response, playing major roles in the recruitment and activation of the immune cells to the inflammatory site, and in the correct development of the adaptive immune response, which determines immunological memory [2]. Homeostatic chemokines are produced under stable conditions and regulate leukocyte migration [3]. However, inflammatory chemokines are mostly produced under pathological conditions and together with pro-inflammatory factors such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), and they actively participate in the inflammatory response that draws immune cells to the injury site [4].

Among the chemokine receptors are the decoy receptors called atypical chemokine receptors (ACKR) which negatively regulate chemokine function. ACKRs contain four types of receptors including ACKR1, ACKR2, ACKR3 and ACKR4 [5]. They are structurally similar to conventional chemokine receptors (cCKR) and can clear, separate and regulate chemokines to control cCKR-induced responses. Thus, they can limit chemokine responses and inflammation [6]. The removal of chemokines and other inflammatory cytokines is critical during resolution of an inflammation and when evaluated together with lymphatic drainage, ACKRs have an important function in this respect [7]. One of these molecules, ACKR2, is a high-affinity receptor for multiple inflammatory CC-chemokines [8].

Lymphatic endothelial cells (LEC) are the most important source of ACKR2 located in small lymphatics, the villi of the small and large intestines, the large common lymphatics located in the lamina propria of the colon and in the muscle layer [9]. ACKR2 clears CC chemokine ligand-2 (CCL2), which is expressed by LECs and is a chemotactic chemokine for monocytes, reducing the accumulation of macrophages, which has a key role in the development of new lymphatics. In this study conducted on mice, it was emphasized that hyper-branched lymphatics developed in ACKR2 deficiency [7].

There are a limited number of studies examining the relationship between gastrointestinal system diseases and ACKR2 in humans, and one found that ACKR2 expression decreased in patients with colon cancer, which was associated with more invasive tumors [10]. In a study conducted on ACKR2-deficient mice infected with Mycobacterium tuberculosis, which is frequently used in the differential diagnosis of CD and causes a granulomatous disease, survival was lower than that in wild type (WT) mice. Also, a higher mononuclear cell count, as well as higher proinflammatory cytokine and CC chemokine levels were detected [11].

Impaired cytokine balance and impaired interactions between antigen presenting cells are considered the key factors in the chronicity of Crohn's disease [12]. Based on this, we planned the first study in the literature researching the relationship between ACKR2, a member of the chemokine family, and Crohn's disease.

Materials and methods

Ethical approval

The study was approved by the Noninvasive Clinical Research Ethics Committee of Kanuni Sultan Suleyman Training and Research Hospital (Decision number: KAEK/2020.06.96, Dated: 06.2020). Informed consents of all patients were obtained.

Study design

Patients with active CD and a Crohn's Disease Activity Index (CDAI) above 150 points, and those referred to our center with a pre-diagnosis of CD between June 2020 and January 2021 were evaluated in this prospective case-control study. All patients with luminal CD confirmed according to the standard criteria were included [13].

Endoscopies were performed by a gastroenterologist using Fujinon Video Colonoscope EC-580RD-L (Fujifilm ™ Europe, Düsseldorf, Germany) colonoscopy devices.

Montreal classification was used to define disease involvement site (L1: Ileal, L2: Colonic, L3: Ileocolonic, L4: Isolated upper disease) and disease behavior (B1: Non-stricturing, non-penetrating, B2: Stricturing, B3: Penetrating, p: Modified perianal disease) [14].

Simplified endoscopic score for Crohn's disease (SES-CD) [15] and CDAI [16] were used to assess disease activation. CDAI score was calculated and recorded electronically on the day of the endoscopy. Blood samples were obtained from the patients for analysis on the same day. The current treatments and additional diseases of the patients were recorded by querying the hospital online data and patient files.

Inclusion and exclusion criteria

Inclusion criteria: Presence of active Crohn's disease meeting the criteria [13].

Exclusion criteria: 1) Patients under the age of 18 years, 2) Crohn's disease in remission, 3) Patients diagnosed with malignancy.

Laboratory tests

Blood samples of the patients were taken into tubes with Ethylenediaminetetraacetic acid (EDTA), and hematological analysis of the samples was performed on the XN-900 (Sysmex™, Japan) device. The biochemistry parameters were analyzed in the SF-8200 (Roche™ Cobas 8000, USA) device with the serum obtained by centrifuging the blood samples taken into the gel tube at 3500 rpm for 10 minutes at room temperature. A part of the sample was immediately separated and stored at -80ºC.

The ACKR2 level was quantitatively determined from the serum samples of the patients stored at -80°C in the central laboratory of the second hospital with the ELISA method (Addcare ELISA 200, P.R. China) using the ELISA kit on the device (SinoGeneClon Biotech, Hangzhou, China-SG-16750). ACKR2 analysis was performed by the method described:

Purified ACKR2 antibody was used to coat the plate, solid phase antibody was made, then ACKR2 was added to the wells, and the ACKR2 antibody was combined with the labeled Horseradish peroxidase (HRP) to form an antibody-antigen-enzyme-antibody complex. After complete washing, Tetramethylbenzidine (TMB) substrate solution was added. TMB substrate turns blue when catalyzed by the enzyme HRP,

the reaction was terminated by adding stop solution and the color change was measured at 450 nm wavelength. The ACKR2 concentration in the samples was then determined by comparing the optical density of the samples with the standard curve.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences v22 (SPSS, Inc, Chicago IL, USA). Conformity of continuous variables to normal distribution was evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk tests). In the descriptive statistics, categorical variables were given as numbers and percentages, data showing normal distribution were presented as arithmetic mean and standard deviations, data not suitable for normal distribution were given as median (minimum-maximum) values. Continuous variables among independent groups were analyzed with the Kruskal Wallis test and the Mann-Whitney U test. Pearson chi-square ($\chi 2$) test was used in the comparison analysis for categorical variables among independent groups. In cases where the variables were not normally distributed, a nonparametric test of Spearman correlation was used instead.

Results

A total of 119 subjects were included in the study, including 66 CDs and 53 healthy controls. The mean age of the control group was 31.56 (7.07) years, and the mean age of CD was 35.89 (11.42) years. Gender distribution in the control (47.2% male, n=25 and 52.8% female, n=28) and the CD groups (77.3% male, n=51 and 22.7% female, n=15) significantly differed (P=0.001).

Clinical findings in CD

In the CD patient group, the number of newly diagnosed and untreated patients was 38 (57.6%) and the number of patients receiving treatment was 28 (42.4%). The median disease duration in the treated group was 3 (1-20) months.

According to the Montreal classification, the disease type and the rates of involvement were as follows: B1 (non-stricturing, non-penetrating: 50%, n= 33), B2 (stricturing: 24%, n = 16), B3 (penetrating: 25%, n = 17), L1 (ileal: 19.7%, n = 13), L2 (colonic: 33%, n = 22) and L3 (ileocolonic: 47%, n = 31). Perianal disease was present in 4.5% (n = 3) of the cases. While 89.4% (n = 59) of the patients did not have any rheumatological disease, 10.6% (n = 7) had an additional rheumatological disease. Of the patients who received treatment, 15 (53.6%) were treated with Azathioprine (AZT), 10 (35.7%) with AZT + anti-TNF, 1 (3.5%) with AZT + steroid and 2 (7.1%) were taking only anti-TNF (Table 1).

Laboratory findings

The comparison between ACKR2 and some laboratory parameters in the control and CD groups is summarized in Table 2. According to the analysis, ACKR2, albumin, hemoglobin and lymphocyte values of the CD group were significantly lower, while CRP, neutrophil and platelet (PLT) counts were significantly higher compared to the controls (P<0.05 for all).

The correlation analysis between ACKR2 and some laboratory parameters, SES-CD and CDAI is summarized in Table 3. There was a weak positive correlation between ACKR2, SES-CD and CDAI (r = 0.350, P=0.004; r = 0.252, P=0.041, respectively), and a weak negative correlation between ACKR2 and albumin (r = -0.253, P=0.040, respectively). No correlation was found between other laboratory parameters and ACKR2 (P>0.05).

Table 1: Clinical findings of the study population

Variables	n (%)
Age (years)	35.89 (11.42)
Females	15 (22.7)
Males	51 (77.3)
Disease location	
L1 (ileal)	13 (19)
L2 (colonic)	22 (33)
L3 (ileocolonic)	31 (47)
L4 (isolated upper GI)	0 (0)
Luminal disease behavior	
B1 (non-stricturing, non-penetrating)	33 (50)
B2 (stricturing)	16 (24)
B3 (penetrating)	17 (25)
Perianal involvement	3 (4.5)
Disease duration, median, (months)*	3 (1-20)
Current smoker	5 (7.57)
Treatment	28 (42.4)
Azathioprine	15 (53.6)
Anti-TNF alfa + Azathioprine	10 (35.7)
Corticosteroids + Azathioprine	1 (3.5)
Anti-TNF alfa	2 (7.1)

Table 2: Comparison of laboratory parameters in CD and control group

	Control (n=53)	CD (n=66)	*P*-value
ACKR2 (ng/mL)	11.15 (3.43-67.08)	4.80 (0.42-23.10)	<0.001
Albumin (g/L)	40.00 (33.00-45.00)	35.50 (24.00-40.00)	<0.001
CRP (mg/L)	0.85 (0.09-5.16)	27.50 (0.60-248.0)	<0.001
Hemoglobin(gr/dL)	13.9 (11.00-16.40)	12.50 (4.90-16.20)	0.001
Platelet ($x10^9$/L)	264 (164-369)	360 (155-791)	<0.001
Neutrophil ($x10^9$/L)	3.53 (1.95-8.71)	6.15 (2.00-16.00)	<0.001
Lymphocyte ($x10^9$/L)	2.30 (1.10-4.70)	1.80 (0.40-3.80)	0.001

Mann-Whitney U test. CD: Crohn's disease, ACKR2: atypical chemokine receptor 2, CRP: C-reactive protein

Table 3: Examining the relationship between ACKR2 and clinical-laboratory parameters

	r	*P*-value
ACKR2		
CDAI score	0.252	0.041
SES-CD score	0.350	0.004
Disease duration (month)	0.092	0.463
Albumin (g/L)	-0.253	0.040
CRP (mg/L)	0.210	0.091
Hemoglobin (gr/dL)	-0.033	0.794
Platelet ($x10^9$/L)	-0.067	0.595
Neutrophil ($x10^9$/L)	0.127	0.308
Lymphocyte ($x10^9$/L)	-0.239	0.053

Spearman correlation analysis. ACKR2: atypical chemokine receptor 2, CDAI: Crohn's disease activity index, SES-CD: simplified endoscopic score for Crohn's disease, CRP: C-reactive protein.

Comparison of serum ACKR2, C-reactive protein (CRP), albumin levels and SES-CD and CDAI scores between the groups according to the Montreal classification is presented in Table 4. In the comparison made according to disease behavior, no statistically significant difference was found between these parameters (P>0.05). Serum ACKR2, CRP and SES-CD scores were significantly lower in the L1 (ileal) group when compared in terms of disease localization (P<0.05).

The median (min-max) ACKR2 levels in the newly diagnosed and treated groups were 4.48 ng/mL (0.42-23.10), and 5.05 ng / mL (1.20-22.08), respectively. According to this analysis, although serum ACKR2 levels were higher in Crohn's patients receiving treatment, the difference was not significant (P=0.673).

Table 4: Comparison of clinical-laboratory parameters according to Montreal classification on CD.

	ACKR2 (ng/mL)		CRP (mg/L)		Albumin (g/L)		CDAI		SES-CD	
	Median (min-max)	*P*-value	Median (min-max)	*P*-value	Median (min-max)	*P*-value	Median (min-max)	*P*-value	Median (min-max)	*P*-value
B1	3.96 (0.42-23.10)	0.076	26.00 (0.60-217)	0.569	36.0 (25.0-40.0)	0.108	210 (160-490)	0.146	7 (4-12)	0.083
B2	6.54 (1.20-22.98)		28.50 (1.00-152)		34.5 (28.0-38.0)		250 (180-460)		9.5 (7-12)	
B3	6.51 (1.70-18.13)		34.00 (3.00-248)		33.0 (24.0-40.0)		310 (180-580)		8 (5-12)	
L1	3.22 (0.42-7.18)	0.002	12.00 (0.60-72.0)	0.010	38.0 (34.0-40.0)	0.066	190 (166-420)	0.104	6 (4-10)	0.029
L2	5.10 (1.81-23.10)		45.00 (1.0-217)		34.0 (25.0-38.0)		233 (160-490)		7.5 (4-12)	
L3	6.51 (1.20-22.98)		32.00 (3.0-248)		34.0 (24.0-40.0)		280 (160-580)		10 (5-12)	

The Kruskal Wallis test was used. CD: Crohn's disease, ACKR2: atypical chemokine receptor 2, CRP: C-reactive protein, CDAI: Crohn's disease activity index, SES-CD: simplified endoscopic score for Crohn's disease, Montreal classification: B1: non-stricturing, non-penetrating, B2: stricturing, B3: penetrating, L1: ileal, L2: colonic, L3: ileocolonic

Discussion

There are important studies investigating autoimmune and inflammatory mechanisms related to ACKR 2. It has become an interesting molecule over time due to its contribution to the regulation of T lymphocyte functions and since it prevents inappropriate accumulation of chemokines and immune cells in inflamed tissues [17].

Mc Kimme et al. stated that ACKR2 in LECs was a necessary molecule for the development of mature dendritic cells and the efficiency of antigen presentation [18].

In a study conducted to investigate susceptibility to autoimmunity, experimental autoimmune encephalomyelitis modeling was performed. It has been reported that in mice with ACKR2 deficiency and disease symptoms, this may occur because of dendritic cell migration and T-cell priming [19].

Hansell et al. stated that ACKR2 deficiency in mice impaired autoreactive T cell priming, could not suppress autoimmune pathology and caused subtle changes in the development of the disease by inducing arthritic and neuropathic autoimmunity [20].

ACKRs also have important roles in the control of inflammatory events. Lymphatic endothelial cells in the skin express ACKR2 to prevent them from being coated with inflammatory chemokines. This is especially important in terms of stopping the leukocytes from accumulating around the vessels and interfering with the flow of tissue fluid and mature dendritic cells [21]. In a study using human dermal LECs, ACKR2 was upregulated by the inflammatory mediators IL-6, type-I interferon (IFN) and IFN- and noted that ACKR2 plays a role in suppressing inflammatory leukocyte binding to lymphatic endothelial surfaces [18]. In an animal model, psoriasiform lesions could be controlled with ACKR2 stimulated by IFN- applied to the lesion edges on the skin. The authors also emphasized that a systemic ACKR2 induction could be used as a therapeutic strategy [22].

In a mouse model of dextran sulfate sodium (DSS)-induced colitis, ACKR2-deficient mice were found to have increased levels of inflammatory chemokines and increased intestinal inflammation, weight loss, and disease activity index compared to WT. In WT mice, on the other hand, ACKR2 was overexpressed by the lymphatic venules and had a protective role against intestinal inflammation [23].

In our study, ACKR2 level was significantly lower in the CD group compared to the control group ($P<0.05$). There was a weak positive correlation between ACKR2 level, SES-CD and CDAI. This shows us that despite the increase in disease activity, there is not enough ACKR2 upregulation. Serum ACKR2 level was significantly lower in the L1 (ileal) group ($P<0.05$). This can be explained by the lower CDAI and SES-CD scores in the L1 group compared to the other groups.

Limitation

Assessment could be more accurate with evaluation of ACKR2 gene polymorphisms among the CD and control groups. Thus, both the effects of ACKR2 deficiency on susceptibility to CD and why it could not be induced at a sufficient level despite the increase in disease activity could be partially answered, and its effects on the course of the disease could be discussed from another perspective. This could be the subject of future research.

Conclusion

ACKR2 level was lower in active CD in our study. This evidence may conclude that ACKR2-mediated chemokine clearance is not sufficient in CD, which has a negative effect on the course of the disease. Given its regulatory role during inflammation and T-cell priming, ACKR2 could be seen as a novel therapeutic target that could be used to suppress chemokine-induced inflammation in chronically inflamed tissues.

References

1. Bachelerie F, Ben-Baruch A, Burkhardt AM, Combadiere C, Farber JM, Graham GJ, et al. International Union of Pharmacology. LXXXIX. Update on the extended family of chemokine receptors and introducing a new nomenclature for atypical chemokine receptors. Pharmacol Rev. 2013 Nov 11;66(1):1-79. doi: 10.1124/pr.113.007724.
2. Mantovani A. Cytokines and their receptors. In: Ratcliffe MJH, editor. Encyclopedia of Immunobiology. Amsterdam: Elsevier; 2016. p. 438-604.
3. Johnston B, Butcher EC. Chemokines in rapid leukocyte adhesion triggering and migration. Semin Immunol. 2002 Apr;14(2):83-92. doi: 10.1006/smim.2001.0345.
4. Balkwill F. Cancer and the chemokine network. Nat Rev Cancer. 2004 Jul;4(7):540-50. doi: 10.1038/nrc1388.
5. Graham GJ, Locati M, Mantovani A, Rot A, Thelen M. The biochemistry and biology of the atypical chemokine receptors. Immunol Lett. 2012 Jul 30;145(1-2):30-8. doi: 10.1016/j.imlet.2012.04.004.
6. Nibbs RJ, Graham GJ. Immune regulation by atypical chemokine receptors. Nat Rev Immunol. 2013 Nov;13(11):815-29. doi: 10.1038/nri3544.
7. Lee KM, Danuser R, Stein JV, Graham D, Nibbs RJ, Graham GJ. The chemokine receptors ACKR2 and CCR2 reciprocally regulate lymphatic vessel density. EMBO J. 2014 Nov 3;33(21):2564-80. doi: 10.15252/embj.201488887.
8. Graham GJ, Locati M. Regulation of the immune and inflammatory responses by the 'atypical' chemokine receptor D6. J Pathol. 2013 Jan;229(2):168-75. doi: 10.1002/path.4123.
9. Nibbs RJ, Kriehuber E, Ponath PD, Parent D, Qin S, Campbell JD, et al. The beta-chemokine receptor D6 is expressed by lymphatic endothelium and a subset of vascular tumors. Am J Pathol. 2001 Mar;158(3):867-77. doi: 10.1016/s0002-9440(10)64035-7.
10. Langenes V, Svensson H, Borjesson L, Gustavsson B, Bemark M, Sjoling A, et al. Expression of the chemokine decoy receptor D6 is decreased in colon adenocarcinomas. Cancer Immunol Immunother. 2013 Nov;62(11):1687-95. doi: 10.1007/s00262-013-1472-0.
11. Di Liberto D, Locati M, Caccamo N, Vecchi A, Meraviglia S, Salerno A, et al. Role of the chemokine decoy receptor D6 in balancing inflammation, immune activation, and antimicrobial resistance in Mycobacterium tuberculosis infection. J Exp Med. 2008 Sep 1;205(9):2075-84. doi: 10.1084/jem.20070608.
12. Shanahan F. Crohn's disease. Lancet. 2002 Jan 5;359(9300):62-9. doi: 10.1016/S0140-6736(02)07284-7.
13. Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis. 2019 Feb 1;13(2):144-164. doi: 10.1093/ecco-jcc/jjy113.
14. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006 Jun;55(6):749-53. doi: 10.1136/gut.2005.082909.
15. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SESCD. Gastrointest Endosc. 2004 Oct;60(4):505-12. doi: 10.1016/s0016-5107(04)01878-4.
16. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976 Mar;70(3):439-44.
17. Bonavita O, Mollica Poeta V, Setten E, Massara M, Bonecchi R. ACKR2: An Atypical Chemokine Receptor Regulating Lymphatic Biology. Front Immunol. 2017 Jan 11;7:691. doi: 10.3389/fimmu.2016.00691.
18. McKimmie CS, Singh MD, Hewit K, Lopez-Franco O, Le Brocq M, Rose-John S, et al. An analysis of the function and expression of D6 on lymphatic endothelial cells. Blood. 2013 May 2;121(18):3768-77. doi: 10.1182/blood-2012-04-425314.

19. Liu L, Graham GJ, Damodaran A, Hu T, Lira SA, Sasse M, et al. Cutting edge: the silent chemokine receptor D6 is required for generating T cell responses that mediate experimental autoimmune encephalomyelitis. J Immunol. 2006 Jul 1;177(1):17-21. doi: 10.4049/jimmunol.177.1.17.
20. Hansell CA, MacLellan LM, Oldham RS, Doonan J, Chapple KJ, Anderson EJ, et al. The atypical chemokine receptor ACKR2 suppresses Th17 responses to protein autoantigens. Immunol Cell Biol. 2015 Feb;93(2):167-76. doi: 10.1038/icb.2014.90.
21. Lee KM, McKimmie CS, Gilchrist DS, Pallas KJ, Nibbs RJ, Garside P, et al. D6 facilitates cellular migration, and fluid flow, to lymph nodes by suppressing lymphatic congestion. Blood. 2011 Dec 1;118(23):6220-9. doi: 10.1182/blood-2011-03-344044.
22. Shams K, Wilson GJ, Singh M, van den Bogaard EH, Le Brocq ML, Holmes S, et al. Spread of Psoriasiform Inflammation to Remote Tissues Is Restricted by the Atypical Chemokine Receptor ACKR2. J Invest Dermatol. 2017 Jan;137(1):85-94. doi: 10.1016/j.jid.2016.07.039.
23. Vetrano S, Borroni EM, Sarukhan A, Savino B, Bonecchi R, Correale C, et al. The lymphatic system controls intestinal inflammation and inflammation-as-sociated colon cancer through the chemokine decoy receptor D6. Gut. 2010 Feb;59(2):197-206. doi: 10.1136/gut.2009.183772.

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Serum galectin-3 levels and vitamin D relationship in heart failure

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Ethics Committee Approval
The study was approved by the Okmeydanı Education and Research Hospital Ethics Committee dated 03/04/2018 and numbered 864.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Heart failure is an important health problem with an increasing incidence in the world and poor prognosis. Galectin-3 is associated with progressive fibrosis, an underlying pathology of heart failure, just as vitamin D deficiency. We examined the relationship between the stage of heart failure and galectin-3 and 25-OH vitamin D levels.
Methods: Sixty patients with heart failure and 30 healthy volunteers were included in this prospective case-control study. Demographic data, comorbid diseases and laboratory data were examined, and 25-OH vitamin D and galectin-3 levels were compared between the patients with CHF and the control group.
Results: Galectin-3 levels were high in patients with heart failure (P<0.001) and increased as the ejection fraction (EF) decreased (P=0.001). 25-OH vitamin D levels were lower in the patient group compared to the control group (P<0.001). There was no significant correlation between serum galectin-3 and vitamin D levels (r=-0.22; P=0.094); however, serum galectin-3 levels and the stage of CHF were correlated (r=0.66; P=0.001).
Conclusions: We found high serum galectin-3 levels in patients with heart failure and low 25 OH vitamin D levels. We think that both molecules are important prognostic biomarkers in cardiac inflammation and fibrosis.

Keywords: Galectin 3, Congestive heart failure, Vitamin D3 level

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Introduction

Heart failure is a complex clinical syndrome characterized by inadequate blood perfusion to the tissues and organs with hemodynamic, renal and neurohormonal effects caused by structural or functional abnormalities in the heart [1]. It is a serious health problem with increasing morbidity and mortality with age [2]. Pump failure due to myocardial contractile disorder is the key factor in heart failure. However, systolic and diastolic dysfunctions of the heart, valvular disorders, vascular and endocrine diseases may also be the cause.

Galectin-3, a member of the lectin family, binds to beta galactoside and weighs 29 to 35 kDa. It is found in the cytoplasm, nucleus and extracellularly in many tissues, especially the myocardium, fibroblasts, endothelial cells, and inflammatory cells such as macrophages, and binds to the cell surface [3, 4]. Studies show that galectin-3 is associated with cardiac fibroblast proliferation, collagen storage and ventricular dysfunction [5, 6]. These changes in the heart lead to a decrease in left ventricular ejection fraction and cardiac output [6].

Vitamin D deficiency has many metabolic effects. Previous studies reported an association between vitamin D deficiency and atherosclerosis, hypertension, heart failure and fibrosis, cardiomyopathy, coronary artery disease and peripheral arterial diseases [7, 8]. It has also been shown that vitamin D deficiency increases the severity of chronic inflammation and is closely related to inflammatory cytokines such as TNF-alpha and interleukin-6 (IL-6), which mediate the development of chronic heart failure [9]. Vitamin D replacement decreases TNF-alpha and IL-6 levels in chronic heart failure [10].

Galectin-3 was shown to have a role in myocardial fibrosis and cardiac failure via cardiac remodeling in a few previous studies. In our study, we investigated the relationship between systolic function, cardiac functional capacity and vitamin D and galectin-3 levels in patients with heart failure at different stages.

Materials and methods

Design and patients

Ninety patients aged between 39-88 years who were admitted to our Internal Medicine Department between 2018 and 2019 were included in our study. Sixty cases with decompensated heart failure formed the patient group and 30 healthy subjects were included as controls. Heart failure was diagnosed according to the European Society of Cardiology guidelines and the group consisted of patients with low and mid-range ejection fractions. Laboratory data and vitamin D and galectin-3 levels were compared between the groups. Heart failure and its duration were classified according to the New York Heart Association (NYHA) criteria [11]. The age, height, weight, BMI values of the patients, concomitant diseases (HT, DM, CHF, hyperlipidemia, COPD, CRF and other), smoking and alcohol use, all of which were recorded in our outpatient clinic, were evaluated for the study.

Two more tube tubes of blood were obtained from the volunteers in addition to the routine laboratory tests during follow-up. After keeping the blood tubes at room temperature for 15 minutes, they were centrifuged for 15 minutes on 4000 rpm and the obtained sera were preserved at -80°C.

Measurements of Galectin-3 and Performance Characteristics of the Galectin-3 and 25-OH-D vitamin Assay

On the day of analysis, the sera were thawed at room temperature. Enzyme-Linked ImmunoSorbent Assay (ELISA) kits were used for serum measurements of Galectin-3. The analytical (linear) measurement range and the minimal detection limit were 42.3 (19.1) ng/mL and 10.2 ng/mL, respectively, for Galectin-3 and 15.1(7.8) mcg/L and 2.8 mcg/L, respectively, for 25-OH vitamin D.

Ethics committee approval

The study was approved by the Ethics Committee of Okmeydanı Training and Research Hospital on 03/04/2018 with the decision number 864.

Statistical analysis

Mean, standard deviation, median, minimum, maximum, frequency and ratio values were used to present the descriptive statistics. The distribution of the variables was assessed with the Kolmogorov-Smirnov test. The independent samples t-test, Kruskal-Wallis, and Mann-Whitney U tests were used to analyze quantitative independent data. In the analysis of qualitative independent data, the Fischer test was used when the Chi-square test conditions were not met. Effect level and cut off were investigated with the ROC curve. The effect level was investigated by univariate logistic regression. SPSS 22.0 program was used for all analyses. The relationship between the two groups was investigated by the Pearson correlation test. All calculated *P*-values were bidirectional and *P*-values of<0.05 were considered significant.

Power analysis

Power analysis was performed with the G-power program. Based on previous data in the literature, for an effect size of 1.39, an alpha error of 5% and a power of 80%, the smallest sample size for each group to represent the population was 24.

Results

Age and gender distribution were similar between the two groups (P=0.408 and P=0.456, respectively). EF and vitamin D levels were lower among the patients compared to the controls while Galectin-3 levels were higher P=0.001 for all). EF values, serum MPV, total cholesterol, HDL-cholesterol, and CRP levels significantly differed between the two groups. Other laboratory parameters (urea, creatinine, AST, ALT, glucose, LDL-cholesterol, triglyceride, sedimentation rate, sodium, potassium, calcium, chloride, phosphorus and other hemogram parameters except MPV) were similar. All demographic data and the results are shown in Tables 1 and 2 and Figure 1.

Although this was a pilot study, a cut-off value of 40 ng/mL for Galectin-3 was significant in the differentiation of CHF patients from the controls [an area under the curve of 0.800 (0.712-0.888)] (Table 3, Figures 2a and 2b).

Table 1: Data of patient group

	Minimum	Maximum	Median	Mean(SD)
Male, n(%)				44(48.9%)
Female, n(%)				46(51.1%)
Age(year)	39.0	88.0	66.5	66.4(8.9)
Ejection Fraction(%)	15.0	65.0	40.0	41.0(14.7)
CHF duration(year)	2.0	20.0	5.0	5.6(3.1)
WBC(µL)	2.4	21.8	8.7	9.3(3.7)
HGB(g/dl)	6.9	17.5	11.6	11.6(2.3)
HTC(%)	20.4	52.3	36.0	35.9(6.5)
PLT(103µL)	79.0	519.0	246.0	252.7(80.7)
MCV(fl)	61.8	106.0	85.1	84.3(8.6)
MPV(fl)	7.6	13.7	10.1	10.2(1.2)
Glucose(mg/dl)	66.0	547.0	135.0	150.2(74.7)
Creatinine(mg/dl)	0.0	1.0	0.5	0.5(0.3)
AST(IU/L)	8.0	958.0	22.0	36.3(99.9)
ALT(IU/L)	3.0	647.0	17.0	30.4(70.5)
CK(IU/L)	12.0	1311.0	74.5	105.1(158)
Total Cholesterol(mg/dl)	41.0	321.0	159.0	162.4(48)
Triglyceride(mg/dl)	41.0	338.0	113.5	134.1(68.7)
HDL(mg/dl)	3.0	74.0	38.0	37.7(14.5)
LDL(mg/dl)	19.0	217.0	92.0	99.0(37)
CRP(mg/dl)	1.0	239.0	13.0	26.4(36.4)
Sedimentation(mm/h)	3.0	87.0	17.0	28.6(23.5)
TSH(mU/L)	0.0	4.1	1.7	1.8(1.1)
Sodium(mmol/L)	130.0	156.0	139.0	138.9(3.6)
Potassium(mmol/L)	3.3	5.7	4.3	4.3(0.6)
Calcium(mg/dl)	6.2	99.0	9.0	10.0(9.5)
Chlorine(mmol/L)	86.0	110.0	99.1	98.9(5.5)
Phosphorus(mg/dl)	1.4	6.0	3.8	3.6(0.6)
Parathormone(pg/ml)	8.9	297.0	64.9	72.7(52.8)
Vitamin D(mcg/L)	2.8	33.6	12.7	15.1(7.8)
Galectin3(ng/mL)	10.2	88.3	36.2	42.3(19.1)

CHF: Congestive Heart Failure

Table 2: Comparisons between groups

	Patient group		Control group		*P*-value
	Mean(SD)	Median	Mean(SD)	Median	
Male, n(%)	31(51.7%)		13(43.3%)		0.456
Female, n(%)	29(48.3%)		17(56.7%)		
Age(year)	66.8(10.8)	67	65.8(2.7)	66	0.408
Ejection Fraction(%)	32.2(9.1)	33.5	58.6(3.8)	60.0	<0.001
WBC(µL)	8.9(3.5)	8.4	10.2(4.0)	8.9	0.174
HGB(g/dl)	11.7(2.4)	11.6	11.4(2.1)	11.3	0.600
HTC(%)	36.4(6.9)	36.2	35.0(5.7)	34.7	0.354
PLT(10^3µL)	251.2(78.8)	247.0	255.7(85.8)	244.0	0.804
MCV(fl)	83.7(8.3)	83.4	85.5(9.2)	86.6	0.356
MPV(fl)	10.4(1.2)	10.3	9.8(1.3)	9.7	0.024
Glucose(mg/dl)	153.9(68.6)	140.5	142.9(86.6)	116.5	0.317
Creatinine(mg/dl)	0.5(0.3)	0.5	0.6(0.2)	0.6	0.590
AST(IU/L)	41.5(121.9)	21.0	25.9(14.5)	22.5	0.461
ALT(IU/L)	31.9(83.5)	17.0	27.4(32.3)	19.0	0.423
CK(IU/L)	113.8(187.9)	72.0	87.6(65.7)	90.0	0.794
Total Cholesterol(mg/dl)	154.6(48.4)	146.5	178.1(44.1)	180.0	0.009
Triglyceride(mg/dl)	128.0(67.2)	107.5	146.1(71.0)	116.0	0.208
HDL(mg/dl)	35.4(14.6)	35.5	42.2(13.4)	40.5	0.038
LDL(mg/dl)	95.9(38.5)	84.0	105.2(33.5)	101.0	0.073
CRP(mg/dl)	30.7(39.8)	14.0	17.9(27.0)	6.2	0.013
Sedimentation(mm/h)	27.8(23.9)	16.0	30.3(25.0)	20.5	0.908
TSH(mU/L)	1.6(1.1)	1.4	2.3(1.1)	2.4	0.009
Sodium(mmol/L)	138.8(3.9)	139.0	139.2(3.0)	140.0	0.304
Potassium(mmol/L)	4.3(0.6)	4.2	4.3(0.5)	4.3	0.904
Calcium(mg/dl)	9.0(0.7)	9.0	11.9(16.5)	9.2	0.483
Chlorine(mmol/L)	98.5(5.7)	98.9	99.7(5.0)	101.9	0.240
Phosphorus(mg/dl)	3.8(0.9)	3.8	3.4(0.9)	3.8	0.236
Parathormone(pg/ml)	82.7(54.3)	72.3	52.5(43.8)	33.4	0.003
Vitamin D(mcg/L)	10.7(4.8)	10.1	23.8(4.8)	24.0	<0.001
Galectin3(ng/ml)	49.2(19.3)	48.1	28.5(8.3)	30.6	<0.001

[m] Mann-Whitney u test/t-t test, [X²] Chi-square test

Table 3: Galectin-3 values in patient and control groups

	Area under the curve	% 95 Confidence interval	*P*-value
Galectin 3	0.823	0.740-0.906	<0.001
Cut-Off Value 40	0.800	0.712-0.888	<0.001
		Sensitivity	60.0%
		Positive Predictive Value	100.0%
		Specificity	100.0%
		Negative Predictive Value	55.6%

Figure 1: Levels of vitamin D and galectin-3 in the patient and control groups

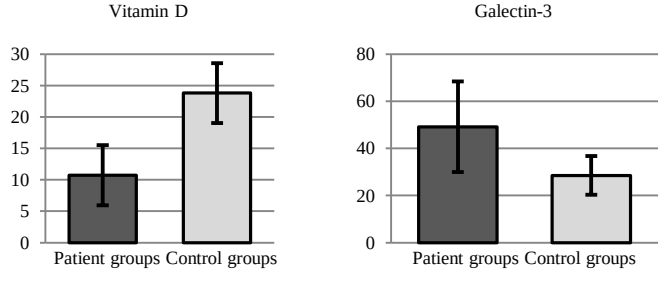
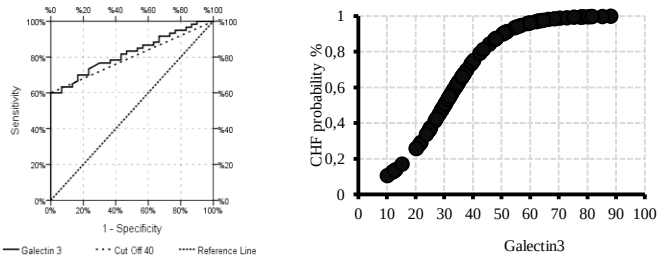


Figure 2a (left) and 2b (right): Galectin-3 values in case and control groups



The relationship between 25-OH vitamin D, Galectin-3 and CHF stage is shown in Table 4. A significant relationship was found between the CHF stage and vitamin D levels in the Kruskal-Wallis test (P=0.011). Galectin-3 levels was significantly correlated with the CHF stage (P=0.001), but not with the age of the CHF patient. The correlation coefficients were -0.01 and 0.66, respectively. Galectin-3 and vitamin D showed no significant correlation (r = -0.22) (Table 5).

Table 4: Levels of 25-OH vitamin D and galectin -3 according to the stages of heart failure

	Min	Max	Median	Mean(SD)	*P*-value
Vitamin D					0.011
Stage I	3.8	20.8	12.2	13.1(4.3)	
Stage II	6.0	30.5	10.4	12.2(6.3)	
Stage III	4.1	16.1	8.7	9.2(3.3)	
Stage IV	2.8	15.5	8.3	8.5(3.7)	
Galectin3					<0.001
Stage I	12.8	56.9	31.9	33.9(12.4)	
Stage II	15.4	81.8	38.2	44.2(17.4)	
Stage III	26.8	72.9	46.8	48.0(13.9)	
Stage IV	51.1	88.3	75.4	70.4(12.8)	

Kruskal-wallis

Table 5: Correlation of Galectin-3 with vitamin D, CHF stage and age of CHF

	r	*P*-value
Vitamin D	-0.22	0.094
CHF stage	0.66	0.001
CHF duration	-0.66	0.511

r: correlation coefficient

Discussion

Galectin 3, a member of the beta-galactoside-binding lectin family, was proven to be a biomarker for mortality in heart failure in many clinical trials [12, 13]. Fibrosis is one of the main mechanisms for heart failure, and Galectin 3 is associated with fibrosis in many organs, particularly the heart [14].

Plasma renin activity is increased in vitamin D deficiency because of renin transcription, which accelerates the course of heart failure. In addition to ACE inhibitors and ARB, vitamin D replacement impedes the progression of heart failure [15].

In our study, we found that galectin-3 levels were higher in patients with heart failure compared to the controls and were correlated with CHF stage.

There was no direct correlation between vitamin D and Galectin-3. However, galectin-3 levels were associated with increased degree of inflammation and fibrosis when the patients were evaluated in terms of NYHA stages, which reveals that galectin-3 could be responsible for the pathogenesis in patients with clinical progression.

In a study of Rossel et al. [16] among hospitalized patients with decompensated heart failure, galectin-3 was increased. Our study was consistent with the meta-analysis data on acute and chronic heart failure [17, 18]. Cho-Kai Wu et al. [19] found that galectin 3 levels were associated with heart failure and myocardial fibrosis in 77 heart failure patients with preserved ejection fraction. A prospective cohort study revealed

that galectin-3 level was an independent predictor of mortality in patients who had chronic heart failure for 26 months when galectin-3 >21 ng/ml [20]. We believe that elevated galectin-3 is not a result but rather, the molecule contributes the process. It is directly proportional to the severity and stage of the disease. In our study, Galectin-3 levels and duration of heart failure were unrelated, and on the contrary, the relationship between the stage of heart failure and the diagnosis of heart failure suggest that this molecule has a direct role in the pathogenesis of the disease.

In addition to its association with plasma renin activity, supplementation of 25-OH vitamin D has been shown to reduce proinflammatory cytokines (TNF-alpha, interleukin -6, IL-1 beta), atherosclerosis and plaque formation and thus plays an important role in the treatment of cardiovascular diseases [21]. Regarding the results of this study, 25-OH vitamin D is thought to play a role in myocardial fibrosis and left ventricular remodeling [22]. Vitamin D deficiency causes secondary hyperparathyroidism, and both primary and secondary hyperparathyroidism are associated with cardiovascular pathologies [23]. In the Tromso study, a relationship was shown between parathormone, calcium and vitamin-D levels and cardiovascular disease [24]. In the Ludwingshafen Risk and Cardiovascular Health Study recently conducted on 3232 patients who underwent angiography, elevated PTH levels were related to cardiovascular death [25]. In our study, 25-OH vitamin D levels were significantly lower in the patient group compared to the control group. As a result, parathormone levels were significantly increased. Increased parathormone level due to vitamin D deficiency worsens the prognosis. The 25-OH vitamin D values were significantly lower among stage III and stage IV patients compared to those with stage I.

In an experimental study, Assalin et al. [26] showed that vitamin D deficiency increased cardiac inflammation, and various cytokines such as tumor necrosis factor (TNF-alpha) and interferon gamma (INF-gamma) caused oxidative stress, increasing left ventricular and atrial fibrosis and apoptosis. The exceptionally low levels of vitamin D in our study group with highly decreased ejection fraction may aggravate heart failure through these cytokines.

Decreased intake, dysfunctional absorption of vitamin D taken orally, less exposure to the sun and outdoor air can explain the lack of vitamin D in these patients. However, considering that heart failure is a process, it would not be wrong to think that the deficiency of vitamin D negatively affects it. This suggests that vitamin D supplementation may be important in patients with heart failure in suppressing cardiac inflammation and decreasing cytokines.

Limitation

The small number of patients was the most important limitation of our study. Further studies are needed with more patient groups.

Conclusion

We found that serum galectin-3 levels increased in patients with heart failure and this elevation was associated with the stage of the disease. Galectin-3 biomarker increases inflammation and fibrosis in heart failure. The association with the clinical stage rather than the duration of heart failure suggests that it may play a role in the pathogenesis of the disease. Similarly, we think that vitamin D deficiency and increased parathormone may be a contributing factor to the process of heart failure and this process can be slowed down by proper replacement. Based on our clinical study, Galectin-3 and 25-OH vitamin D may be involved in the pathophysiology of heart failure and will contribute significantly to the development of new therapies.

References

1. Poole-Wilson PA. History, Definition and Classification of Heart Failure. Heart Failure 1 New York: Churchill Livingstone.1997; p269–277.
2. NICE. Chronic Heart Failure. National Clinical Guidelines for Diagnosis and Management in Primary and Secondary Care. The National Collaborating Centre for Chronic Conditions. London: NICE. 2005;(5):1-163.
3. Dumic J, Dabelic S, Flögel M. Galectin: an open-ended story. Biochim Biophys Acta.2006;(1760):616-635
4. Kim H, Lee J, Hyun JW, Park JW, Joo HG, Shin T. Expression and immunohistochemical localization of galectin 3 in various mouse tissues. Cell Bio Int. 2007;(31):655-62.
5. de Boer RA, Voors AA, Muntendam P, van Gilst WH, van Veldhuisen DJ. Galectin-3: a novel mediator of heart failure development and progression. Eur J Heart Fail. 2009;(11):811-81.
6. Sharma UC, Pokharel S, van Brakel TJ, et al. Galectin-3 in Patients with Heart Failure Reflects Both Inflammation and Fibrosis: Implıcations for Its Use as a Biomarker. Circ Heart Fail. 2017;(10):e003804.
7. Holick MF. Vitamin D deficiency. N Eng J Med. 2007;357(3):266-81.
8. Anderson JL, May HT, Horne BD, Bair L Tami, Hall L Nathaniel, Carlquist F John, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status and incident events in a general healthcare population. Am J Cardiol 2010;(106):963-8.
9. Gullestad L, Ueland T, Vinge LE, Finsen A, Yndestad A, Aukrust P. Inflammatory cytokines in heart failure: mediators and markers. Cardiology. 2012;122(1):23–35.
10. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2006;83(4):754–9.
11. Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.
12. De Boer RA, Voors AA. Galectin-3: a novel mediator of heart failure development and progression. Eur J Heart Fail. 2009;(11):811–7.
13. Ho JE, Liu C. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. J Am Coll Cardiol. 2012;(60):1249–56.
14. LeBleu V. S, Teng Y, O'Connell J.T., Charytan D., Muller G.A., Muller C.A., et al. Identification of human epididymis protein-4 as a fibroblast-derived mediator of fibrosis. Nat Med. 2013;(19):227-31.
15. Schoreten F, Ruifrok WP, Kleijn L, Dokter MM, Silljé HH, Lambers Heerspink HJ, Bakker SJ, Kema IP, van Gilst WH, van Veldhuisen DJ, Hillege HL, de Boer RA. Short term vitamin D3 supplementation lowers plasma renin activity in patientswith stable chronic heart failure: an open-label, blinded end point, randomizedprospective trial (VitD-CHF trial). Am Heart J. 2013 Aug;166(2):357-64.
16. Rossel V, Díaz-Toro F, Verdejo H, Concepción R, Sepúlveda L, Castro P, et al. Galectina-3: experiencia en pacientes chilenos con diagnóstico de insuficiencia cardíaca descompensada [Galectin-3 levels in patients hospitalized for decompensated heart failure]. Rev Med Chil. 2017 Jun;145(6):734-740. Spanish. doi: 10.4067/s0034-98872017000600734. PMID: 29171621.
17. Schindler EI, Szymanski JJ, Hock KG, Geltman EM, Scott MG. Short- and long-term biologic variability of galectin-3 and other cardiac biomarkers in patients with Stable heart failure and healthy adults. Clin Chem. 2016;(62):360–6. doi: 10.1373/clinchem.2015.246553
18. Chen A, Hou W, Zhang Y, Chen Y, He B. Prognostic value of serum galectin-3 in patients with heart failure: A meta-analysis. Int J Cardiol. 2015;(182):168–170. doi: 10.1016/j.ijcard.2014.12.137.
19. Cho-Kai Wu, Mao–Yuan M. Su, Yi-Fan Wu, Whang Juey Ju. Combination of Plasma Biomarkers and Clinical Data for the Detection of Myocardial Fibrosis or Aggravation of Heart Failure Symptoms in Heart Failure with Preserved Ejection Fraction Patients. Journal of Clinical Medicine November 2018;(7):427.
20. Medvedeva EA, Berezin II, Surkova EA, Yaranov DM, Shchukin YV. Galectin-3 in patients with chronic heart failure: Association with oxidative stress, inflammation, renal dysfunction and prognosis. Minerva Cardioangiol. 2016; (64):595–602.
21. Vikrant Rai, Devebdra K. Agrawal Endocrinol Metab Clin N Am (2017);(46):1039-59.
22. Michael P. Dorsch, Carrie W. Nemerovski, Vicki L. Ellingrod, Jennifer A Cowger, D. Bradley Dyke, Todd M. Koelling, et al. Journal of Cardiovascular Pharmacology and Therapeutics. 2014;(5):439-45.
23. Wallis DE, Penckofer S, Sizemore GW. The ''sunshine deficit'' and kardiovascular disease. Circulation 2008; (118):1476-85.
24. Kamycheva E, Sundsfjord J, Jorde R. Serum parathyroid hormone levels predict coronary arter disease: The Tromso Study. Eur J Cardiovasc Prevent Rehabil. 2004;(11):69-74.
25. Pilz S, Tomaschitz A, Drechsler C, et al. Prathyroid hormone level is associated with mortality and cardiyovascular events in patients undergoing coroner angiography. Eur Heart J. 2010;(31):1591-8.
26. Assalin HB, Rafacto BP, dos Santos PP, et al. Impact of the length of vitamin D deficiency on cardiac remodelling. Circ Heart Fail. 2013;6(4):809-16.

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Does intratympanic Mesna application prevent cholesteatoma? An experimental study on rats

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Ethics Committee Approval
The study protocol was approved by the ethics committee of Dicle University Animal Experiments Local Ethics Committee with the decision no. 2013/5.
The study was conducted in line with the Guide for the Care and Use of Laboratory Animals issued by the National Institutes of Health, Commission on Life Sciences, and National Research Council.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Cholesteatoma is an invasive and destructive disease, responsible for most of the complications related to chronic otitis media. The only effective treatment is surgical excision. Researching medical treatment alternatives can bring a new perspective to the treatment of this disease. This study aimed to investigate the effect of Mesna on otitis media and cholesteatoma induced by propylene glycol on an experimental animal model.
Methods: The study was designed to consist of sixteen Wistar albino rats, with their right ears being the control group and the left ears being the experiment group. Fifty percent propylene glycol, gentamicin sulfate, and physiologic saltwater were administered to the right ear, and 50% propylene glycol, gentamicin sulfate, and 20% Mesna were administered to the left ear through intratympanic injections on days 1, 3, 8, 15, and 21. The rats were sacrificed 45 days after the first injection and underwent histopathological examination.
Results: Cholesteatoma and fibrosis were less common in the experimental group. In the study group, the average and maximum thicknesses of the tympanic membranes (P=0.008) and the minimum thicknesses of the tympanic bulla (P=0.019) were significantly less than those of the control group.
Conclusion: In the experimental cholesteatoma model created in rats, Mesna, administered intratympanically, was seen to completely prevent the formation of cholesteatoma. However, histopathological examination revealed that although present, cholesteatoma formation and fibrosis were significantly less in the experimental group.

Keywords: Mesna, cholesteatoma, Fibrosis, Otitis media, Intratympanic

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Introduction

Various studies were published on the development of otitis media and cholesteatoma after the intratympanic application of chemicals on laboratory animals [1-3]. In the 1980s, the eye and ear drop called Cortisporin was observed to cause inflammatory changes and cholesteatoma in the middle ear because of the 10% propylene glycol used as a solvent [4]. In the following years, propylene glycol was used in experimental studies on otitis media and cholesteatoma because of its inflammatory effect on the ear [5-7]. Sodium 2-mercaptoethanesulfonate (C2 H 5 NaO 3S 2, Mesna) is a synthetic sulfur compound that carries a thiol group. It breaks the disulfide bonds in a polypeptide chain with mucolysis. The matrix of the cholesteatoma or squamous epithelial is made of keratin, a protein with disulfide bonds. Mesna can be used to ease the dissection of the tissue layers in the surgery of cholesteatoma due to its mucolytic properties [8]. Studies reported that the administration of Mesna to the middle ear cavity does not affect hearing [9, 10]. For this reason, we planned to investigate the effect of Mesna on cholesteatoma and otitis media created in the middle ear cavity of experimental animals by propylene glycol. We aimed to show the presence of keratinized epithelium in the middle ear, the inflammatory changes in the middle ear mucosa, and the changes in the morphology of the tympanic membrane through histopathological evaluation.

Materials and methods

The study was conducted in line with the Guide for the Care and Use of Laboratory Animals issued by the National Institutes of Health, Commission on Life Sciences, and National Research Council [11]. The study protocol was approved by the Dicle University Animal Experiments Local Ethics Committee (10/10/2013/5)

Experimental animals

Sixteen healthy male Wistar albino rats weighing between 210-304 grams with healthy outer ear canals and tympanic membrane in otoscopic examination were used in our study. All experimental animals were housed in appropriate cages under standard environmental conditions (room temperature 22^{o}C-24^{o}C, 50% relative humidity, and 12-hour periods of light-dark). The animals could access water and a traditional laboratory diet until they were sacrificed.

Experimental design

The study was designed to have the right ears of the rats as the control group and the left ears as the experimental group.

Propylene glycol was used to form a cholesteatoma and an inflammatory reaction in the middle ear mucosa. Mesna was used to inhibit the pathologic processes in the middle ear mucosa and gentamicin was utilized to inhibit the inflammatory process caused by sulfate. Intratympanic injections were administered to all rats on the pars tensa region of the tympanic membrane on days 1, 3, 8, 15, and 21 under a surgical microscope. Each ear underwent 5 administrations in total. The rats were sacrificed 45 days after the first injection.

Solutions used in the control group (right ear): 0.2 ml 50% propylene glycol, 0.1 ml gentamicin sulfate (40 mg/ ml) and 0.1 ml physiologic salt water (0.9%).

Solutions used in the experimental group (left ear): 0.2 ml 50% propylene glycol, 0.1 ml gentamicin sulfate (40 mg/ ml) and 0.1 ml 20% Mesna (100mg/ ml).

Anesthesia

All rats were anesthetized with intramuscular 60 mg/kg ketamine hydrochloride and 10mg/kg 2% xylazine hydrochloride.

Tissue preparation and histopathological examination

All procedures were conducted under hygienic, albeit nonsterile conditions. The animals were sacrificed after anesthesia and the tympanic membrane and tympanic bulla were removed with microdissection. The specimens were fixed for 24 hours in 10% formaldehyde solution. Then they were decalcified for one week in a 10% formic acid solution. After the fixation and decalcification procedures, the specimens were transversely cut into two, dehydrated in baths of alcohol and a tissue tracking procedure was implemented. Then, they were buried in paraffin. Cross-sections with a thickness of 5 microns were taken, which were dyed with hematoxylin and eosin and examined under a light microscope (Zeiss Axiophot Axioplan, Germany) by a single expert pathologist. In the examination, the tympanic membrane and the middle ear mucosa were evaluated according to various pre-determined histopathological properties (presence of inflammatory cells, presence of fibrosis, presence of keratinized epithelium in the middle ear (cholesteatoma), thickness of the tympanic membrane, thickness of the tympanic bulla mucosa). The thicknesses of the tympanic membrane and tympanic bulla were measured under a 10x magnification.

Statistical analysis

Data analyses were performed with the Statistical Package for the Social Sciences (SPSS for Windows, version 15.0) software. Fisher's exact tests were used in the investigation of the relationships between parameters. For nonparametric data, Mann Whitney *U* test was performed. $P<0.05$ was considered statistically significant.

Results

The results were evaluated qualitatively and quantitatively.

Qualitative results

In the control group, the tympanic membrane was intact in 10 of the 16 ears, and not intact in 6. Inflamed cells were present in the tympanic membrane of 1 ear and the tympanic bulla mucosa of 2 ears. A small number of inflamed cells were present in the tympanic membrane, while a significant amount of inflamed cells were observed in the tympanic bulla mucosa. It was noted that almost all inflamed cells consisted of polymorphonuclear leukocytes. Cholesteatoma was seen in 8 ears, and fibrinous-proteinosis material was observed in 3.

In the experimental group, the tympanic membrane was intact in 8 of the 16 ears, and not intact in 8. Cholesteatoma was seen in 7 ears (Figures 1-2). Obvious inflammation and fibrosis were not observed in the tympanic membrane and tympanic bulla mucosa.

Figure 1: Development of keratinized epithelium and cholesteatoma in the middle ear in the control group. Thin arrow = tympanic membrane, disc = keratinized stratified squamous epithelium (i.e. cholesteatoma), thick arrow = tympanic bulla mucosa (H & E; × 10)

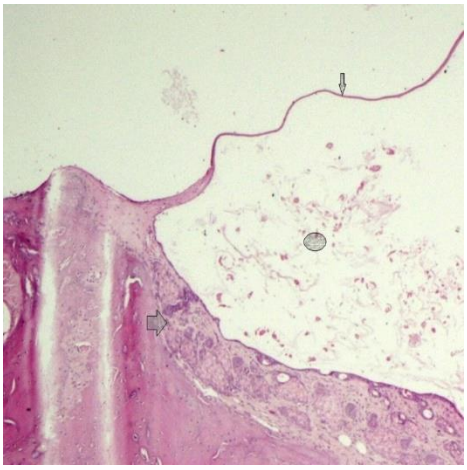
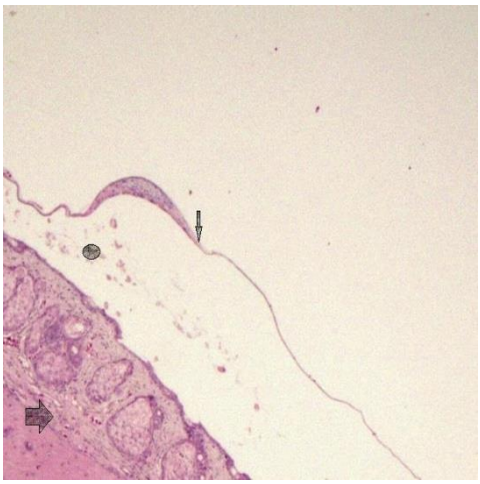


Figure 2: Development of keratinized epithelium and cholesteatoma in the middle ear in the experimental group. Thin arrow = tympanic membrane, disc = keratinized stratified squamous epithelium (i.e., cholesteatoma), thick arrow = tympanic bulla mucosa (H & E; × 10)



The two groups were similar regarding the prevalence of cholesteatoma and fibrosis (P=0.08). Meanwhile, microscopic histopathological evaluation revealed that the prevalence of cholesteatoma and fibrosis was lower in the experimental group.

Quantitative results

The tympanic bulla mucosa and tympanic membrane thicknesses of the experiment group and the control group were measured (Tables 1 and 2). The minimum mucosal thickness of the tympanic bulla (P=0.019), as well as the maximum and average thicknesses of the tympanic membrane were significantly less in the experimental group compared to the control group (P=0.008, P=0.011, respectively).

Table 1: Statistical analysis of groups according to the thickness of the tympanic membrane

Groups	Ears(n)	Tympanic membrane thicknesses(μm)		
		Minimum	Maximum	Mean
Experiment	11	0.3927	1.1409	0.7482
Control	11	0.5045	3.1791	2.6745

Table 2: Statistical analysis of groups according to the tympanic bulla mucosal thickness

Groups	Ears(n)	Tympanic bulla mucosa thicknesses (μm)		
		Minimum	Maximum	Mean
Experiment	12	2.2333	14.8733	12.6400
Control	12	3.6208	22.7408	19.1200

Discussion

In the recent years, Mesna is being used in surgical procedures for tissue dissection because of its chemical properties [12]. In the practice of otolaryngology, it aids in dissecting the thickness between the tympanic membrane and the middle ear mucosa in adhesive otitis media and atelectatic tympanic membranes [8, 13]. Yılmaz et al. [8] conducted a study where they administered Mesna to 42 ears of 39 patients with retraction pockets fixed to the incudostapedial joint, stapes, or promontorium who had adhesive otitis media and reported that the use of Mesna is safe and eases the surgery, increasing surgical success. In their retrospective study, Kalcioğlu et al. [13] reported that the use of Mesna increases surgical success, decreasing the need for second-look surgery. In our clinic, we usually use 20% Mesna in the surgery of adhesive otitis media. We administer Mesna from the non-retracted region of the tympanic membrane or the antrum to the middle ear cavity and usually use dental injectors to administer one dose. We wait for approximately 4-6 minutes after administration.

Different agents have been used to prevent the development of experimental cholesteatoma. Various studies report that cyclophosphamide, isotretinoin, hyaluronic acid, and mitomycin–C have no inhibiting effect on the development of cholesteatoma. Prednisolone, trans-retinoic acid, 5- fluorouracil have been reported to stop the increase of cholesteatoma [6, 14-17]. In our study, we administered Mesna to inhibit the cholesteatoma that occurred with the intratympanic injection of propylene glycol, and according to the histopathological evaluation, it succeeded.

Based on the theory of epithelial migration, propylene glycol causes cholesteatoma [4, 7]. However, the studies regarding the prevalence of cholesteatoma formation and histopathological properties report varying results. Experimental studies showed that proliferation of the epithelial basal layer of the tympanic membrane starts in the third week [18, 19]. In the sixth week, the prevalence of cholesteatoma caused by 90% propylene glycol (90%) is 87.5% [20]. In the tympanic bullae of chinchilla-type rats, a single application of 50% propylene glycol can form a cholesteatoma after three weeks [4]. The concentration of the mucosal irritant used to form experimental cholesteatoma and the duration of use are important. We used 50% propylene glycol in our study and sacrificed the rats 45 days after the first administration. The cholesteatoma prevalence of 50% in our control group was in concordance with the studies in the literature (33–90%) [5]. The cholesteatoma was mainly located at the tympanic bulla. Melo et al. [5] showed that epidermal invasion extends from the tympanic membrane to the tympanic bulla.

A study conducted on Wistar rats emphasized that single dose intratympanic Mesna prevented the formation of cholesteatoma [21]. In our study, despite the intratympanic Mesna administration five times, no significance was found, indicating that the cholesteatoma was completely prevented. However, in microscopic examination, Mesna was observed to reduce the prevalence of cholesteatoma and fibrosis.

Limitations

Ours is a single-center study which was conducted with a limited number of Wistar albino rats. Further studies with more subjects in which appropriate laboratory conditions are provided are needed to clarify the effect of Mesna on cholesteatoma. The researchers can investigate the most effective dose, or the optimal number of administrations.

Conclusion

According to the histopathological results of our study, the intratympanic administration of Mesna decreased the prevalence of cholesteatoma.

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References

1. Rüedi L. Cholesteatoma formation in the middle ear in animal experiments. Acta Otolaryngol. 1959 May-Aug;50(3-6):233-40. doi: 10.3109/00016485909129191
2. Hueb MM, Goycoolea MY, Muchow D, Duvall AJ, Paparella MM, Sheridan C. In search of missing links in otology. III. Development of a new animal model for cholesteatoma. Laryngoscope.1993 Jul;103:774-84. doi: 10.1288/00005537-199307000-00011.
3. Piltcher OB, Swarts JD, Magnuson K, Alper CM, Doyle WJ, Hebda PA. A rat model of otitis media with effusion caused by eustachian tube obstruction with and without Streptococcus pneumonia infection: methods and disease course.Otolaryngol Head Neck Surg. 2002 May;126(5):490-8. doi: 10.1067/mhn.2002.124935.
4. Masaki M, Wright CG, Lee DH, Meyerhoff WL. Effects of Otic Drops on Chinchilla Tympanic Membrane. Arch Otolaryngol Head Neck Surg.1988 Sep;114:1007-11. doi: 10.1001/archotol.1988.01860210073019
5. Melo AA, Caldas Neto SS, Leão FS, Campos AJ. Effect of intratympanic mitomycin C on the development of cholesteatoma and otitis media in rats. J Laryngol Otol.2013 Apr;127(4):359-63.doi: 10.1017/S002221511300011X
6. Sennaroglu L, Ozkul A, Gedikoglu G, Turan E. Effect of intratympanic steroid application on the development of experimental cholesteatoma.Laryngoscope.1998;108:543-7. doi: 10.1097/00005537-199804000-00015
7. Antunes ML, Fukuda Y, PenidoNde O, Ferreira R. Effect of trans-retinoic acid in the inhibition of cholesteatoma in guinea pigs. Rev Bras Otorrinolaringol. 2008 Jan-Feb;74(1):53-60. doi: 10.1016/s1808-8694(15)30751-5
8. Yilmaz M, Goksu N, Bayramoglu I, Bayazit YA. Practical use of MESNA in atelectatic ears and adhesive otitis media. ORL J Otorhinolaryngol Relat Spec. 2006 Feb; 68(4):195-8. doi: 10.1159/000091472
9. Vincenti V, Mondain M, Pasanisi E, Piazza F, Puel JL, Bacciu S, et al. Cochlear effects of MESNA application into the middle ear. Ann N Y Acad Sci.1999 Nov;884:425-32. doi: 10.1111/j.1749-6632.1999.tb08659.x.
10. Van MP, Timmermans JP, Claes J, Scheuermann DW, Wuyts FL, Van de Heyning PH. Single ototopical application of MESNA has no ototoxic effects on guinea pig cochlear hair cells: a morphological study. Acta Otolaryngol.1999;119(6):685-9. doi: 10.1080/00016489950180630.
11. Institute of Laboratory Animal Research. Commission on Life Sciences. National Research Council. The guide for the care and use of laboratory animals. 7th ed. Washington DC: National Academies Press; 1996.
12. Casale M, Di Martino A, Salvinelli F, Trombetta M, Denaro V. Mesna for chemically assisted tissue dissection. Expert Opin Investig Drugs. 2010 Jun;19:699-707. doi: 10.1517/13543784.2010.485192.
13. Kalcioglu MT, Cicek MT, Bayindir T, Ozdamar OI.Effectiveness of mesna on the success of cholesteatoma surgery. Am J Otolaryngol Head Neck Surg. 2014 May-Jun;35 (3): 357-61. doi: 10.1016/j.amjoto.2014.01.002
14. Pownell PH, Wright CG, Robinson KS, Meyerhoff WL. The effect of cyclophosphamide on development of experimental cholesteatoma. Arch Otolaryngol Head Neck Surg. 1994 Oct;120:1114-6. doi: 10.1001/archotol.1994.01880340058009
15. Jove MA, Vassalli L, Raslan W, Applebaum EL. The effect of isotretinoin on propylene glycol-induced cholesteatoma in chinchilla middle ears. Am J Otolaryngol. 1990 Jul-Aug;11:5-9. doi: 10.1016/0196-0709(90)90163-p
16. White SJ, Wright CG, Robinson KS, Meyerhoff WL. Effect of topical hyaluronic acid on experimental cholesteatoma. Am J Otolaryngol. 1995 Sep-Oct;16:312-8. doi: 10.1016/0196-0709(95)90059-4.
17. Wright CG, Bird LL, Meyerhoff WL. Effect of 5-fluorouracil in cholesteatoma development in an animal model. Am J Otolaryngol. 1991 May-Jun;12(3):133-8. doi: 10.1016/0196-0709(91)90142-3.
18. Masaki M, Wright CG, Lee DH, Meyerhoff WL. Experimental cholesteatoma: epidermal ingrowth through tympanic membrane following middle ear applications of propylene glycol. Acta Otolaryngol (Stockh).1989 Jul-Aug;108(1-2):113-21. doi: 10.3109/00016488909107401.
19. Huang CC, Shi GS, Yi ZX. Experimental Induction of middle ear cholesteatoma in rats. Am J Otolaryngol. 1988 Jul-Aug;9(4):165-72. doi: 10.1016/s0196-0709(88)80024-3.
20. Vassalli L, Harris DM, Gradini R, Applebaum EL. Propylene Glycol-Induced Cholesteatoma in Chinchilla Middle Ears. Am J Otolaryngol. 1988 Jul-Aug;9(4):180-8. doi: 10.1016/s0196-0709(88)80026-7.
21. Ismi O, Karabulut YY, Bal KK, Vayisoglu Y, Unal M. Single dose intratympanic mesna application inhibits propylene glycol induced cholesteatoma formation. J Laryngol Otol.2017 Mar;131(3):215-20. doi: 10.1017/S002221511600983X.

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Investigation of work-related tension levels and related factors in healthcare workers

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Ethics Committee Approval
This study was initiated with the approval of Van Yüzüncü Yıl University Non-Invasive Clinical Research Ethics Committee (Decision No: 2019/04-05, Date: 22/02/2019).
The data of this study were taken from the specialist thesis of the responsible author. (Department of family medicine, specialty thesis, Yüzüncü Yıl University, Van, Turkey)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Factors such as heavy workload and infectious diseases cause Work-Related Tension (WRT) in healthcare workers. This study aimed to evaluate the Work-Related Tension Scale (WRTS) scores of healthcare workers to assess whether they are concerned about infecting their families and themselves as a result of their work and whether they are thinking about being fired or changing professions if they have this anxiety.

Methods: A total of 300 healthcare professionals working in a university hospital were included in this cross-sectional study. Data were obtained with the work-related stress scale (WRTS) and descriptive questionnaire and analyzed using SPSS 20.0 software. A $P<0.05$ was considered statistically significant. Descriptive statistics and ANOVA analysis were used during statistical evaluation.

Results: The mean WRTS score (yes: 42.71) of the participants who had anxiety about infecting their families because of their jobs was significantly higher than that of the other groups (partially: 41.49, no: 38.16) ($P<0.001$). The mean WRTS score (yes: 42.27) of the participants who had anxiety about infecting themselves was significantly higher than those who did not (partially: 40.9, no: 38.21) ($P=0.012$). Healthcare workers who wanted to resign due to this concern had a considerably higher mean WRTS score (yes: 43.70) than those who wanted to keep working (partially: 42.93, no: 39.86) ($P<0.001$).

Conclusion: Healthcare workers are concerned about infecting themselves and their families because of their jobs. As a result of this concern, their WRT levels are increased, and they are alienated from their work. Measures to increase effective protection against infectious diseases and stress management are needed.

Keywords: Healthcare workers, Work-related tension, Contagiousness anxiety

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Introduction

The healthcare sector is considered to have elevated job stress, and work-related tension is experienced more often than in the other professions because of both providing service to the patients and their relatives who are experiencing intense stress, and frequent encounters with stress sources [1-3]. Factors such as heavy workload, giving care to patients with poor general conditions, and emotionally supporting the patients and their relatives can cause work-related tension (WRT) among the healthcare workers. WRT and burnout syndrome are mostly seen in professions that provide service to people such as medicine, nursing, and physiotherapy. Problems arise when the frequency and duration of the work exceed the individual's coping ability. It can also reduce productivity, job satisfaction, punctuality, and increase resignations [4, 5].

Infectious diseases occur due to a microorganism or their harmful products. They can occur after direct or indirect transmission of an agent from the infected individual, animal, or reservoir to a susceptible host by an animal host, vector, or lifeless environment [6]. Healthcare professionals are at the risk of encountering many infectious agents in their working environment. For the occurrence of any nosocomial infection, a focus, a susceptible host, and a route of transmission are required. Blocking the transmission route between the focus of infection and the host may help prevent infection in both the patients and the healthcare personnel [7]. As in the current Covid-19 pandemic, the pathogens can remain suspended in the air and airborne viruses, or bacteria-infected droplets can spread when someone sneezes or coughs [8]. It is of great importance that the hospitals are kept clean so that patients, their relatives, and healthcare professionals can receive or provide health services in a cleaner environment. Prevention of hospital-acquired infections can be facilitated by cleaning practices and the use of personal protection products and devices. This process includes addressing the basis of the subject, continuing education, and the healthcare professionals and institutions acquiring various habits to provide better service to patients [9, 10]. While it is known that health workers, especially doctors, experience high levels of work stress even at normal times, the Covid-19 virus pandemic caused additional pressure on the health system all around the world [11]. The theoretical and practical (stress coping techniques) training the physicians will receive about managing the intense stress in our country is necessary for their professional success [12]. Healthcare workers can stop worrying about infecting themselves and their families because they work at a hospital. In addition, the resignation of qualified health workers may also be prevented.

Literature review showed that various studies related to the WRT level of health workers were carried out all around the world in recent years. Our study aimed to determine whether the relationship between the stress experienced by healthcare workers due to their job and their approach to nosocomial infections show significant differences according to socio-demographic and occupational characteristics.

Materials and methods

This cross-sectional descriptive study was conducted with the participation of 300 volunteering healthcare professionals (doctor, nurse/health officer, emergency medical technician, paramedic, laboratory worker, health technician, nurse, and cleaning staff, etc.) working in a university hospital between March and June 2019.

The sample size was calculated using the equation $n=z^2.\delta^2/d^2$ to represent the population of the study (n = 860).

The survey consists of a socio-demographic information form prepared by the researchers, a questionnaire of 44 questions measuring the level of knowledge about infectious diseases and protection. WRTS, which comprises 18 “fill in the blanks” and multiple-choice questions, is the "Work-related tension scale" developed by Revicki et al. [13] in 1991, and the Turkish validity and reliability study was performed by Aslan et al. [4] in 1996. It is a 4-point Likert-type self-report scale containing 18 items developed to determine work-related tension and stress in healthcare workers. The scoring is as follows: 4 = Strongly agree 3 = Mostly agree 2 = Partially agree 1 = Disagree. The 2^{nd}, 4^{th}, 8^{th}, 9^{th}, $11^{th,}$ and 15^{th} questions are scored in reverse. The lowest and highest scores are 18 and 72, respectively. A high total score indicates increased work-related tension.

This single-center study was initiated with the approval of Van Yüzüncü Yıl University Non-Invasive Clinical Research Ethics Committee (Decision No: 2019/04-05, Date: 22/02/2019) and conducted following the Declaration of Helsinki. The participants were informed about the study, and their verbal and written consents were obtained.

Statistical analysis

Chi-square test was used for descriptive statistics and the continuous variables were expressed as mean, standard deviation, minimum and maximum. Categorical variables were expressed as numbers and percentages. One-way analysis of variance was used to compare group means of continuous variables. Duncan, LSD, Tukey, Games-Howell multiple comparison tests were used to identify the different groups following the analysis of variance. The statistical significance level was 5% and the SPSS statistical package program was used for all calculations.

Results

The patients’ ages, genders, marital and educational statuses, professional experience (years), working hours per week, current departments, and occupation were presented in Tables 1 and 2. Among all, 56% were male, 60% were married, 35.3% were between the ages of 30-35 years, 64% had a university degree or higher. Seventy-two percent of the participants had less than 10 years of professional experience and 86% of the participants were working for 40 hours or more per week. Most participants were working in the Internal Diseases and surgical clinics.

Among the participants, those who had the anxiety of infecting their families because of working in a hospital had significantly higher WRTS scores than the other groups (P<0.001). The mean WRTS score of the participants who had anxiety about contagion was significantly higher than that of the other groups (P=0.012). Those who stated that they were

dismissed from their jobs due to this anxiety had higher average WRTS scores than the other groups (P<0.001) (Table 3).

Table 1: Gender, marital status, age, and educational status characteristics of the participants (n=300)

Features	Categories	n	%
Gender	male	169	56.3
	female	131	43.7
Marital Status	Married	180	60.0
	Single	107	35.7
	Widowed / Divorced	13	4.3
Age Range	18-25	47	15.7
	26-29	75	25.0
	30-35	106	35.3
	36-41	39	13.0
	42 and over	33	11.0
Education Status	Primary Education	6	2.0
	Secondary Education	24	8.0
	High school	78	26.0
	University	91	30.3
	Doctorate	101	33.7
Total		300	100

Table 2: Participants' professional experience (years), weekly working hours (hours), current department and occupational information characteristics (n=300)

Features	Categories	n	%
Professional experience (years)	1-5	126	42
	6-10	90	30
	11-15	42	14
	16-20	27	9
	21 and over	15	5
Weekly working time (hours)	20-30	5	1.7
	30-40	37	12.3
	40-50	151	50.3
	50-60	24	8
	60 and above	83	27.7
The department they are currently working in	Internal clinic	86	28.7
	Surgical clinic	60	20
	Pediatrics clinics	44	14.7
	Polyclinic and intervention rooms	36	12.0
	Emergency	28	9.3
	Intensive care unit	16	5.3
	Blood center	6	2.0
	Operating room	5	1.7
	Hemodialysis unit	3	1
	Laboratory	16	5.3
Profession	Doctor	101	33.7
	Nurse/paramedic	99	33
	Housekeeper/caregiver	100	33.3
Total		300	100

Table 3: Examination of the scores of the participants according to their anxiety to infect their families or themselves and the state of being dismissed from their jobs

Features	n	WRTS*			P-value*
		Average	Std. deviation	Min / Max	
Do you worry about infecting your family with a contagious disease because of your work? (n = 300)					
Yes	139	42.71	6.81	29/60	0.001
Partially	105	41.49	7.18	25/59	
No	56	38.16	8.72	21/64	
Do you worry about being infected with a contagious disease because of your work? (n = 300)					
Yes	182	42.27	7.14	28/60	0.012
Partially	85	40.90	7.76	21/64	
No	33	38.21	7.88	23/56	
Have you been alienated from your job because of this anxiety? (n = 266)					
Yes	65	43.70	6.95	30/60	0.001
Partially	93	42.93	6.60	28/59	
No	108	39.86	7.75	21/64	

*: One-way variance analysis and Duncan, WRTS: Work-Related Tension Scale

Discussion

Cai et al. [14] found that concerns about personal health and infecting their families were the main factors triggering work-related stress among the healthcare workers in China. In the study conducted by Dai et al. [15], one of the main concerns of health workers was infecting their family members (63.9%). The mean WRTS score of the health workers included in our study was higher among those who were worried about infecting their family members because of their job. According to the literature review, there is a relationship between such an anxious state and the WRT levels.

Alimoğlu et al. [16] found a significant difference between WRT levels and emotional exhaustion, while there was no significant relationship between the participants' work-related health problems and WRT levels. In the study of Tokuç et al. [17], the average WRTS score of participants, who use drugs due to an infectious disease that was thought to be transmitted from a patient in the last year, was higher than that of the other groups. In addition to the general stress factors that Chinese health workers are exposed to, they experience anxiety due to the risk of infecting themselves and the others due to COVID-19 [18]. There is a connection between the WRT level of healthcare workers and their anxiety about spreading a work-related infection. In our study, similar to others, a significant difference was found between the mean WRTS score of healthcare workers who were anxious about infecting themselves with work-related infections and those who were not.

Erçevik et al. [19] reported that the average WRTS score of nurses who would not re-choose their profession was higher than those who would or those who did not want to change jobs at all. In a study by Arıkan et al. [20] conducted in 2003, 69.3% of the participating nurses stated that they would choose another profession if they had a second chance. The mean WRTS scores of the nurses who wanted to change their profession were higher than those who would want to continue the same profession. Aslan et al. [21] researched the validity and reliability of the work-related tension scale in the healthcare sector in 1998 and found that the mean WRTS score was higher among the participants who stated that they would choose another profession if they graduated from high school today. In the study conducted by Vatansever [22] in 2016, a significant relationship was found between the participants' choice of profession/department and the mean WRTS score. The mean WRTS score was higher among those who are thinking of changing professions. Our study yielded similar results with the literature. The average WRTS score was higher among those who were thinking of changing their profession and who stated that they were alienated from their current job. Although it can be concluded that those who are considering a job change are not satisfied with their current jobs, it has recently been found that healthcare workers in our country are considering a job change due to the low professional reputation and financial gain and the increased violence in health.

Limitations and strengths of the study

One of the strongest aspects of our study is that it was conducted before the Covid-19 pandemic, which proved that healthcare workers already had anxiety about infectious disease transmission. Its cross-sectional and single-center design is our study's main limitation. It is recommended that similar multi-center studies be conducted with more participants.

Conclusion

Healthcare workers had concerns about infecting themselves and their families because of their jobs. They had elevated WRT levels, and they did not want to continue working in their current profession because of this anxiety.

The Covid-19 pandemic that occurred after the completion of our study proved our rationale. We would recommend using novel technology that will reduce the possibility of disease transmission routinely in all healthcare institutions.

The possibility of infecting family members can be reduced by disinfecting the clothes of employees after work or working with appropriate uniforms provided by the hospital management. Increasing the number of employees, especially in risky departments such as intensive care units, and arranging weekly working hours per the world standards will also reduce work-related tension and positively affect health outcomes.

References

1. Boswell CA. Work stress and job satisfaction for the community health nurse. Journal of Community Health Nursing. 1992;9(4):221-7.
2. Clegg A. Occupational stress in nursing: a review of the literature. Journal Of Nursing Management. 2001;9(2):101-6.
3. Sultana A, Sharma R, Hossain MM, Bhattacharya S, Purohit N. Burnout among healthcare providers during Covid-19: Challenges and evidence-based interventions. Indian J Med Ethics. Published online on 2020 July 4;1:1-4 DOI:10.20529/IJME.2020.73.
4. Aslan H, Aslan O, Kesepara C, Alparslan N, Ünal M. Kocaeli'nde bir grup sağlık çalışanında işe bağlı gerginlik, tükenme ve iş doyumu. Toplum ve Hekim. 1997;12(82):24-9.
5. Beyoğlu MM, Kuşaslan DA. Examination of the relationship between health literacy, concern, and anxiety in adults with diabetes mellitus or hypertension and comparison with individuals without chronic disease. Journal of Surgery and Medicine. 2020;4(6):456-9.
6. Bakanlığı TS. Temel Sağlık Hizmetleri Genel Müdürlüğü Bulaşıcı Hastalıkları Daire Başkanlığı. HIV/AIDS Surveyans verileri. Ankara: T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü Bulaşıcı Hastalıklar Dairesi Başkanlığı, 2004.
7. Baykam N. Sağlik çalişanlarina temas, enteral ve damlacik yoluyla bulaşan infeksiyonlar ve korunma yollari. Sağlik çalişanlarinin sağliği 1. Ulusal kongresi. Ankara: 1999; p. 62.
8. Wu J, Ping Z. Association of COVID-19 Disease Severity with Transmission Routes and Suggested Changes to Community Guidelines. Preprints 2020, 2020030246 (doi: 10.20944/preprints202003.0246.v1).
9. Alan S. Hastane enfeksiyonlarindan korunmada birimlerin yapilanma. havalandirma, temizleme ve dezenfeksiyon esaslari, hastane enfeksiyonlari: Korunma Ve Kontrol Sempozyum Dizisi. 2008;(60):221-37.
10. Kumar PS, Dhanapal CK, Ravı S, et al. Prevention and control of infections. international Journal of Pharma and Bio Sciences. 2011;(2):145-54.
11. Galbraith N, Boyda D, McFeeters D, Hassan T. The mental health of doctors during the COVID-19 pandemic. BJPsych Bulletin. 2021;45(2):93-7.
12. Sarp N. Hekim ve stres yönetimi. Ankara Üniversitesi Tip Fakültesi Mecmuasi. 2000;53(2):133-7.
13. Revicki, Dennis A, MAY, Harold J, Whıtley, Theodore W. Reliability and validity of the Work-Related Strain Inventory among health professionals. Behavioral medicine. 1991;17(3):111-20.
14. Cai H, Tu B, Ma J, Chen L, Fu L, Jiang Y, et al. Psychological impact and coping strategies of frontline medical staff in Hunan between January and March 2020 during the outbreak of coronavirus disease 2019 (COVID-19) in Hubei, China. Medical Science Monitor: International Medical Journal Of Experimental And Clinical Research. 2020;26:e924171-1.
15. Dai Y, Hu G, Xiong H, Qiu H, Yuan X. Psychological impact of the coronavirus disease 2019 (COVID-19) outbreak on healthcare workers in China. MedRxiv. 2020;1:1-22.
16. Alimoglu MK, Donmez L. Daylight exposure and the other predictors of burnout among nurses in a university hospital. International Journal of Nursing Studies. 2005;42(5):549-55.
17. Tokuç B, Turunç Y, Ekuklu G. Edirne'de ambulans çalişanlarinin anksiyete, depresyon ve işe bağli gerginlik düzeyleri. TTB Mesleki Sağlık ve Güvenlik Dergisi. 2011;11(42):39-44.
18. Inter-Agency Standing Committee, et al. Briefing note on addressing mental health and psychosocial aspects of COVID-19 Outbreak- Version 11. 2020.
19. Erçevik R. Hemşirelerde işe bağlı gerginlik, tükenmişlik düzeyleri ve etkileyen faktörler. Yüksek Lisans Tezi. Haliç Üniversitesi, Sağlık Bilimleri Enstitüsü, Hemşirelik Ana Bilim Dalı; 2010.
20. Arikan D, Karabulut N. Hemşirelerde işe bağli gerginlik ve bunu etkileyen faktörlerin belirlenmesi. Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi. 2004;7(1):10-7.
21. Aslan SH, Alparslan ZN, Aslan RO, Kesepara C, Ünal M. İşe bağlı gerginlik ölçeğinin sağlık alanında çalışanlarda geçerlik ve güvenirliği. Düşünen Adam. 1998;11(2):4-8.
22. Vatansever İ. Trakya Üniversitesi Sağlık Uygulama ve Araştırma Merkezinde çalışan araştırma görevlilerinde işe bağlı gerginlik düzeylerinin değerlendirilmesi. Uzmanlık Tezi, Trakya Üniversitesi Tıp Fakültesi, Aile Hekimliği Anabilim Dalı; 2016.

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The impact of MRI findings in the liver in the diagnosis of pediatric Wilson's disease

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The study was approved by the local Ethics Committee of the University of Health Sciences, Inonu University (approval number: 2021/1648, data:09.02.2021).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Wilson's Disease (WD) is one of the genetic diseases that can be successfully managed with early diagnosis and treatment. There is no single test used in its diagnosis; therefore, the diagnosis is made by laboratory and clinical findings, as well as genetic analysis results. This study aimed to describe the magnetic resonance imaging (MRI) findings in the livers of pediatric patients with WD and evaluate the relationship between serum ceruloplasmin, 24-hour urinary copper values, and MRI findings.
Methods: A total of 35 patients with WD younger than 18 years of age were included in this cohort study. Qualitative and quantitative parameters were evaluated in MRI. The qualitative parameters included parenchymal nodule, contour irregularity, honeycomb pattern, ascites, and increased periportal thickness. The quantitative parameters were splenomegaly and the ratio of the caudate lobe to the right lobe (CL/RL). All patients were classified according to the absence or presence of qualitative and quantitative parameters on MRI. The serum ceruloplasmin levels and 24-hour urinary copper values were evaluated according to the scoring system developed at the Eighth International Meeting on Wilson disease in Leipzig, in 2001. All qualitative and quantitative MRI findings were compared among patients with high and low serum ceruloplasmin levels and 24-hour urinary copper values.
Results: Ascites and splenomegaly were the most common findings, seen in 17 (48.6%) and 19 (52.7%) patients, respectively. Twenty-eight (80%) patients had normal caudate-lobe to the right-lobe (CL/RL) ratio in MRI. The serum ceruloplasmin levels in patients with parenchymal nodules, irregular liver contours, ascites in the abdomen, increased periportal thickness and splenomegaly were significantly lower than those without these findings ($P<0.05$). The 24-hour urinary copper values in patients with ascites and increased periportal thickness were significantly higher than in those without ($P<0.05$).
Conclusion: In case of nonspecific liver MRI findings such as parenchymal nodules, irregular liver contours, ascites in the abdomen, increased periportal thickness, and a normal caudate to right-lobe (CL/RL) ratio in a pediatric patient with decreased serum ceruloplasmin and increased 24-hour urinary copper values, WD should be considered among the causes of chronic liver disease.

Keywords: Wilson disease, Magnetic resonance imaging, Liver, Ceruloplasmin

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Introduction

Wilson disease (WD) is an autosomal recessive disease that occurs due to a defect in copper metabolism, and its prevalence is 1:30.000. In this disease, copper accumulates in various tissues including the liver and the brain due to impaired excretion of copper through bile [1, 2]. WD is one of the genetic diseases that can be successfully managed with early diagnosis and standard treatment. Early diagnosis is of great importance for the prognosis of this disease [3]. There is no single test used in the diagnosis of WD; therefore, the diagnosis is made by laboratory tests and clinical findings, as well as genetic analysis results. According to the scoring system which was developed at the Eighth International Wilson's Disease Meeting held in Leipzig in 2001, 4 points and above was considered sufficient for diagnosis [4]. Abnormal 24-hour urinary copper and serum ceruloplasmin values are also used in this scoring system alongside a few other clinical and laboratory data.

Imaging findings for the liver in WD generally reflect liver damage related to fat infiltration, acute hepatitis, chronic active hepatitis, and cirrhosis [5-8]. Nodular infiltrations and contour abnormalities in the liver were reported in the literature [5-9]. Although studies on liver imaging in WD are on ultrasound (US) and Computed Tomography (CT), only a few are on MRI [6, 7, 10].

We aimed to describe the liver MRI findings in pediatric WD patients, evaluate the relationship between 24-hour urinary copper levels, serum ceruloplasmin values and the MRI findings, and show the contribution of MR imaging to the diagnosis.

Materials and methods

The study complied with the guidelines of the Health Insurance Portability and Accountability Act. Informed consent was obtained from the parents of the patients. This study was approved by the İnönü Üniversity Ethics Committee on 09/02/2021 with the decision number 2021/1648.

A total of 35 patients (20 male, 15 female) younger than 18 years of age who were followed up in the pediatric gastroenterology clinic with the diagnosis of WD between 2006 and 2020 were included in our study. The scoring system, which was developed in Leipzig in 2001, at the Eighth International Meeting on WD was used for the diagnosis of WD. WD was considered if the score was 4 and above [4].

The serum ceruloplasmin levels were evaluated in 3 groups.

Group 1: A normal serum ceruloplasmin value (>0.2 g/dl).
Group 2: A ceruloplasmin value of 0.1 g/dl - 0.2 g/dl.
Group 3: A ceruloplasmin value of <0.1 g/dl.

The urinary copper values were evaluated in 3 groups:
Group 1: A normal urinary copper value (<100 µg).
Group 2: A urinary copper value of 100µg-200µg.
Group 3: A urinary copper value of >200µg.

MR images

The 1.5T (Siemens, Magnetom-Avanto) device was used for MRI. The studies included the following MR sequences: An axial T2-weighted fast spin-echo sequence, an axial T1-weighted fast spin-echo sequence, a coronal fat-suppressed true fast imaging TRUFI (True Fast Imaging with steady-state-free precession) sequence, unenhanced in-and out-of-phase fat-suppressed TSE sequence, and fat-suppressed gradient-echo sequences after intravenous administration of a gadolinium chelate.

A pediatric radiologist reviewed the MRI examinations over the picture archiving and communication system (PACS).

The qualitative parameters examined in MRI were the presence of parenchymal nodules, contour irregularity, a honeycomb pattern, ascites, and increased periportal thickness. The quantitative parameters were splenomegaly and the ratio of the caudate lobe to the right lobe (CL/RL). Per the description of Awaya et al. [11], the right portal vein was used as a landmark in the separation of the caudate and the right lobe for the calculation of CL/RL. A CL/RL value of >0.90 indicated caudate lobe enlargement [11]. The length of the spleen was measured in the coronal plane and values above the upper limit of normal for a particular age group were considered splenomegaly [12].

Statistical analysis

All qualitative and quantitative MRI findings were compared between three groups each, based on the serum ceruloplasmin and 24-hour urinary copper values. SPSS 22 program was used to analyze the data and *P*-values were calculated using the Chi-square test.

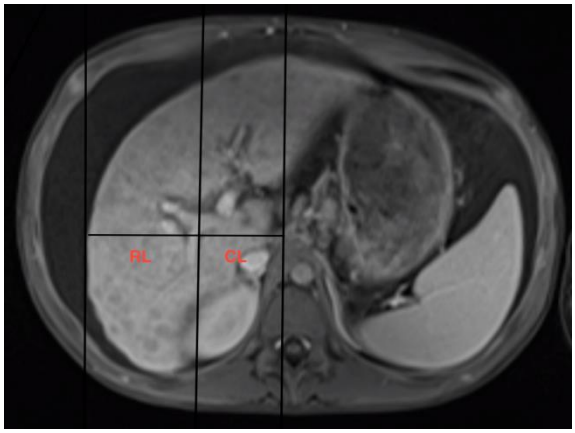
Results

There were 35 patients in our study, twenty (57.1%) males and 15 (42.9%) females. The mean age of the patients was 11.28 years. There was no significant difference between the genders according to the serum ceruloplasmin levels and 24-hour urinary copper values.

The mean serum ceruloplasmin levels and 24-hour urinary copper values were 0.12 g/dl and 378.35µg, respectively. Serum ceruloplasmin level was >0.2 g/dl in 5 (14.2%) patients and 24-hour urinary copper value was <100 µg in 10 (28.5%) patients.

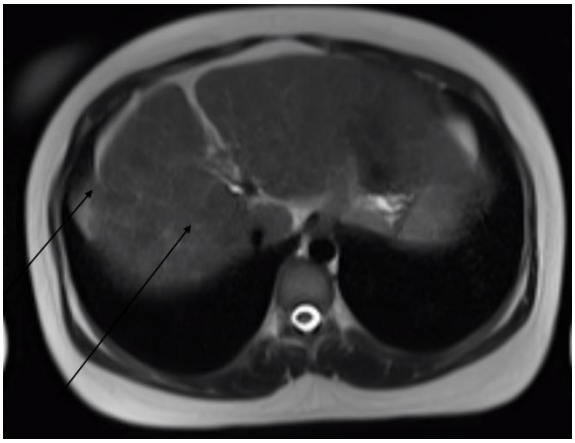
Twenty-eight (80%) patients had normal CL/RL (Figure 1). Splenomegaly was observed in 19 (52.7%) patients, contour irregularity (Figure 2), in 17 (48.6%), ascites (Figure 3), in 17(48.6%), increased periportal thickness (Figure 4) in 12 (35.2%), parenchymal nodules, in 10 (28.6%) and the honeycomb pattern (Figure 3) were seen in 4 (11.4%).

Figure 1: T1-weighted fat-suppressed transverse image



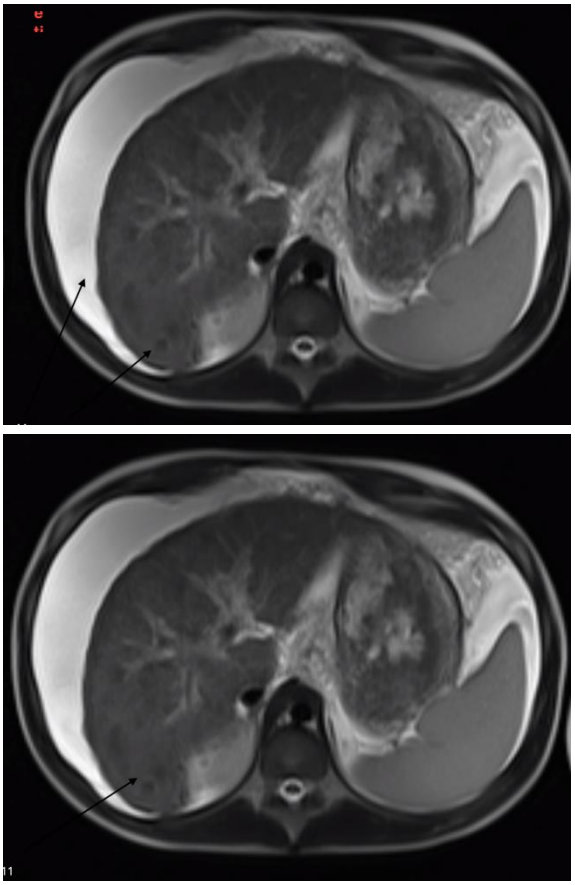
A 14-year-old male with liver cirrhosis and ascites. The MR image obtained in the transverse plane after intravenous administration of a gadolinium chelate shows the calculation method of caudate lobe-to-right lobe ratio (CL/RL). CL indicates the width of the caudate lobe (38 mm). RL is the width of the right lobe (51 mm). In this patient, CL/RL = 0.74.

Figure 2: T2 weighted- transverse image



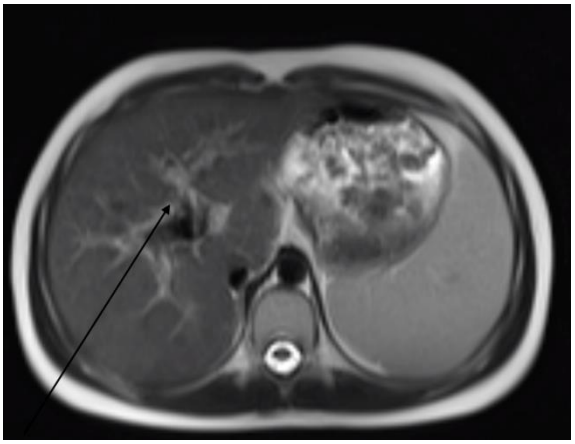
An 8-year-old male with liver cirrhosis had contour irregularity of liver surface and multiple hypointense nodules (shown with arrows).

Figure 3: T2-weighted transverse image, A: Ascites and multiple hypointense nodules (shown with arrows), B: Hyperintense septa (shown with arrows)



A 16-year-old female had ascites in the abdomen and a honeycomb pattern with multiple hypointense nodules surrounded by hyperintense septa.

Figure 4: T2-weighted transverse image



A 7-year-old female had periportal thickening in the liver because of fibrosis (shown with an arrow).

MRI findings of the groups according to the serum ceruloplasmin and urinary copper values are shown in Tables 1 and 2.

Table 1: MRI findings of the patients in the grouping made according to the serum ceruloplasmin values

	Group 1	Group 2	Group 3	Total patients
Parenchymal nodule	0	4(40%)	6(60%)	10(28.6%)
Contour irregularity	0	8(47%)	9(53%)	17(48.6%)
Honeycomb pattern	0	2(50%)	2(50%)	4(11.4%)
Ascites	0	8(47%)	9(53%)	17(48.6%)
Increased periportal thickness	0	4(33.3%)	8(66.6%)	12(35.2%)
Splenomegaly	1(5.2%)	8(42.1%)	10(57.9%)	19(54.3%)

Group 1: Urinary copper value was normal (<100 µg), Group 2: Urinary copper value was 100µg - 200µg, Group 3: Urinary copper value was >200µg

Table 2: MRI findings of the patients in the grouping made according to the 24-hour urinary copper values

	Group 1	Group 2	Group 3	Total patients
Parenchymal nodule	0	2(20%)	8(80%)	10(28.6%)
Contour irregularity	0	6(35.3%)	11(64.7%)	17(48.6%)
Honeycomb pattern	0	1(25%)	3(75%)	4(11.4%)
Ascites	0	7(41.1%)	10(58.9%)	17(48.6%)
Increased periportal thickness	1(%)	2(16.6%)	9(83.4%)	12(35.2%)
Splenomegaly	3(%)	8(50%)	8(50%)	19(54.3%)

Group 1: Urinary copper value was normal (<100 µg), Group 2: Urinary copper value was 100µg - 200µg, Group 3: Urinary copper value was >200µg

Ceruloplasmin levels in patients with parenchymal nodules (P=0.038), irregular liver contours (P=0.005), ascites in the abdomen (P=0.027), splenomegaly (P=0.025) and increased periportal thickness (P=0.02) were significantly lower than in those without. No significant difference was found in terms of the presence of the honeycomb pattern and hypertrophy of the caudate lobe between the patient groups according to serum ceruloplasmin values (P>0.05).

The 24-hour urine copper values in those with ascites in the abdomen (P=0.021) and with an increased periportal thickness (P=0.04) were significantly higher than in those without.

Discussion

There are few studies in the literature about liver MRI findings in WD in childhood. The mean age was 11.28 years in our study, which was the lowest mean age in the literature among the studies on WD. In a study discussing the US, CT, and MRI findings of WD, the mean age was 16 years [5]. The mean age was 14 years in the study of Cheon et al. [6]. The number of male patients was higher in our study, which is compatible with the literature [13].

Copper accumulation in the liver occurs in the periportal regions and hepatic sinusoids in the early stages of the WD [14]. Subsequently, periportal inflammation, necrosis, fibrous inflammatory cell infiltration, and irreversible cirrhosis occur [15]. The differences in the liver imaging findings of WD are associated with the stage of the disease [7]. Many nonspecific imaging findings of liver cirrhosis were described in WD. The honeycomb pattern and normal CL/RL ratio were shown as specific findings [5,6]. Akhan et al. first reported that the caudate lobe is not hypertrophied in WD, unlike other causes of cirrhosis [5]. In our study, consistent with the literature, the CL/RL ratio was normal in 80% (28) of the patients. Liver MRI with the imaging findings of liver cirrhosis but a normal CL/RL ratio should suggest WD, especially in pediatric patients.

Honeycomb pattern was defined as the appearance of hypointense nodules surrounded by hyperintense septa in T2-weighted sequences [8]. The reason for this pattern is still not fully understood and it was reported even in a 2-year-old

asymptomatic patient [16]. The honeycomb pattern was observed in 42% of the patients in the study of Akhan et al. and it was reported as a specific finding in WD [5]. However, it can be seen in other chronic liver diseases such as viral hepatitis [10]. In our study, the honeycomb pattern was observed in only 6 (17.1%) patients. Compared with the literature, our study had the lowest number of patients with the honeycomb pattern. This may be because our study included pediatric patients only.

The irregular contour developing due to parenchymal necrosis and regeneration in the liver was observed in 48.6% of our patients. This rate was 50% in the study of Akhan et al. [5], 62% in the study of Cheon et al. [6], and 36% in the study of Vargas et al. [10]. Irregular contour has high sensitivity in indicating chronic liver disease [17]; however, it is not specific for WD. Ascites is seen in liver cirrhosis, especially in the advanced stages of the disease. While ascites was seen in 48.6% of patients in our study, it was found in only 7% of the patients in the study of Cheon et al. and 8.6% of the patients in the study of Vargas et al. The high rate of ascites in this study can be explained with the high number of end-stage liver disease patients referred for transplantation to our hospital, which is one of the leading liver transplantation centers in the world.

Increased periportal thickness is one of the early-stage imaging findings of liver cirrhosis [5]. Akhan et al. observed this finding in 67.9% of their patients in ultrasound, but they found that this rate was much lower in MRI. In our study, 35.2% of the patients had increased periportal thickness, which was higher than the other studies in the literature on ascites. Parenchymal nodules in WD, which are seen in the liver MRI, develop due to copper accumulation and the nodules are generally hypointense on T2-weighted images [5]. This finding was reported between 40-50% in the literature [5,6]. Parenchymal nodules were quite low compared to the literature in our study. Ko et al. claimed that this finding can be observed in the early period in WD [18]. This may be the reason why our results were lower than those in the literature.

Serum ceruloplasmin values are generally <200 mg/L in WD, except for an exceedingly small proportion [19]. In the largest study in the literature about the role of biochemical measurements in the diagnosis of WD, serum ceruloplasmin values were low in all 715 WD patients and ceruloplasmin value was found to have high sensitivity in diagnosis [20]. The 24-hour urinary copper value is another biochemical measurement used in WD and it is significant for diagnosis if it exceeds 100 µg [19]. However, its sensitivity is lower compared to the serum ceruloplasmin value. Although these biochemical tests are especially important in the diagnosis, the definitive diagnosis of the disease cannot be based on them alone. MRI evaluation showed that patients with parenchymal nodules, irregular liver contours, ascites in the abdomen, splenomegaly and increased periportal thickness had lower serum ceruloplasmin values than patients without. These findings are nonspecific for WD, but they correlate with serum ceruloplasmin values. Ascites and increased periportal thickness correlate with 24-hour urinary copper values.

Our study had some limitations. First, it was a retrospective study. The MRI variables were not evaluated in terms of interobserver reliability. Also, the patients were a heterogeneous group in terms of the treatment they received during MRI examination, which may affect the MR images.

Conclusion

Although serum ceruloplasmin and 24-hour urine copper values are included in diagnostic scoring, supportive findings are needed for early diagnosis. In case of nonspecific liver MRI findings such as parenchymal nodules, irregular liver contours, ascites in the abdomen and increased periportal thickness, a normal CL/RL in the liver MRI with decreased serum ceruloplasmin and increased 24-hour urinary copper values in children, WD should be considered among the causes of chronic liver disease.

References

1. European Association for Study of Liver (EASL) Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56:671–85.
2. Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML. Wilson's disease. Lancet. 2007;369:397–408.
3. Bandmann O, Weiss KH, Kaler SG. Wilson's disease and other neurological copper disorders. Lancet Neurol. 2015;14:103–13.
4. Roberts EA, Schilsky ML. American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. Hepatology. 2008;47:2089-111.
5. Akhan O, Akpinar E, Karcaaltincaba M, Haliloglu M, Akata D, Karaosmanoglu AD, et al. Imaging findings of liver involvement of Wilson's disease. Eur J Radiol. 2009;69:147–55.
6. Cheon JE, Kim IO, Seo JK, Ko JS, Lee JM, Shin CI, et al. Clinical application of liver MR imaging in Wilson's disease. Korean J Radiol. 2010;11:665–72.
7. Akhan O, Akpinar E, Oto A, Köroglu M, Ozmen MN, Akata D, et al. Unusual imaging findings in Wilson's disease. Eur Radiol. 2002;12:S66–9.
8. Tokuhisa Y, Shimizu M, Yachie A. Honeycomb appearance of the liver in Wilson's disease. Clin Gastroenterol Hepatol. 2012;10:A25.
9. Kozic D, Svetel M, Petrovic I, Sener RN, Kostic VS. Regression of nodular liver lesions in Wilson's disease. Acta Radiol. 2006;47:624-7.
10. Vargas O, Faraoun SA, Guerrache Y, Woimant F, Hamzi L, Boudiaf M, et al. MR imaging features of liver involvement by Wilson disease in adult patients. Radiol Med. 2016;121:546-56.
11. Awaya H, Mitchell DG, Kamishima T, Holland G, Ito K, Matsumoto T. Cirrhosis: modified caudate-right lobe ratio. Radiology. 2002;224:769–74.
12. Konus OL, Ozdemir A, Akkaya A, Erbas G, Celik H, Işik S. Normal liver, spleen, and kidney dimensions in neonates, infants, and children: evaluation with sonography. AJR Am J Roentgenol. 1998;171:1693–8.
13. Manolaki N, Nikolopoulou G, Daikos GL, Panagiotakaki E, Tzetis M, Roma E, et al. Wilson disease in children: analysis of 57 cases. J Pediatr Gastroenterol Nutr. 2009;48:72-7.
14. Mergo PJ, Ros PR, Buetow PC, Buck JL. Diffuse disease of the liver: radiologic-pathologic correlation. Radiographics. 1994;14:1291-307.
15. Cope-Yokoyama S, Finegold MJ, Sturniolo GC, Kim K, Mescoli C, Rugge M, et al. Wilson disease: histopathological correlations with treatment on follow-up liver biopsies. World J Gastroenterol. 2010;16:1487-94.
16. Vogl TJ, Steiner S, Hammerstingl R, Schwarz S, Kraft E, Weinzierl M, et al. MRT of the liver in Wilson's disease. Rofo. 1994;160:40–5.
17. Colli A, Fraquelli M, Andreoletti M, Marino B, Zuccoli E, Conte D. Severe liver fibrosis: accuracy of US for detection-analysis of 300 cases. Radiology. 2003;227:89–94.
18. Ko S, Lee T, Ng S, Lin J, Cheng Y. Unusual liver MR findings of Wilson's disease in an asymptomatic 2-year-old girl. Abdom Imaging. 1998;23:56–9.
19. Roberts EA, Schilsky ML. American Association for Study of Liver Diseases. Diagnosis and treatment of Wilson disease: an update. Hepatology. 2008;47:2089–111.
20. Dong Y, Wang R.M, Yang G.M, Yu H, Xu WQ, Xie JJ, et al. Role for Biochemical Assays and Kayser-Fleischer Rings in Diagnosis of Wilson's Disease. Clinic Gastroentrol Hepatol. 2020;S1542-3565:30751-5.

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Gynecological natural orifice transluminal endoscopic surgeries from an anesthesiologist's perspective: A retrospective cohort study

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Abstract

Background/Aim: Natural orifice transluminal endoscopic surgical (NOTES) approach allows either transgastric or transvaginal access to the targeted organs by endoscopes without a skin incision. This study aimed to evaluate the intraoperative and postoperative outcomes of patients who underwent vaginally assisted NOTES (VaNOTES) for gynecological surgery.

Methods: One hundred ten patients who underwent hysterectomy and/or bilateral salpingo-oophorectomy (BSO) under general anesthesia either with conventional laparoscopy (CL) or VaNOTES methods were examined. The data of the patients were obtained from the medical records retrospectively. Demographic data, perioperative hemodynamic data, Visual Analogue Scale (VAS) scores, and analgesic consumption at the 1st, 6th, and 24th postoperative hours were assessed.

Results: Among all patients, the median duration of anesthesia, median operation time, and hospital stay were lower in the VaNOTES group compared to those in CL (P<0.001). The change in perioperative hemodynamic findings was similar in both patient groups. While the median VAS scores were lower in the VaNOTES group at the 6th and 24th postoperative hours in patients with BSO (P=0.024 and P=0.021), those of patients who underwent hysterectomy were lower at the 1st postoperative hour (P=0.002). However, the change in VAS scores was similar in both patient groups. In addition, no postoperative complications or mortality were observed in any of the groups.

Conclusion: Application of NOTES technique in gynecological operations may contribute to the reduction of invasive procedures, shorten the duration of surgery and anesthesia, lower pain severity, and improve hospital stay postoperatively.

Keywords: Gynecologic surgery, Natural orifice transluminal endoscopic surgery, Pain assessment

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Introduction

The natural orifice transluminal endoscopic surgical (NOTES) approach allows either transgastric or transvaginal access to the targeted organs by endoscopes without any skin incision [1, 2]. NOTES is associated with minimal surgical trauma, early patient mobilization, less postoperative pain, and better cosmetic results in cholecystectomy, appendectomy, hysterectomy, and salpingo-oophorectomy procedures [2].

NOTES requires CO_2 insufflation and steep Trendelenburg position, both of which are necessary to adequately visualize the abdominal and thoracic cavity, as is also the case in the conventional laparoscopic approach [3]. From the viewpoint of anesthesiologists, this new technique provides benefit to respiratory functions perioperatively due to less intraabdominal pressure requirement, shortening of the operation time, decreased need of perioperative analgesia, and a lower angular Trendelenburg angle. In a randomized controlled trial, the results of the NOTES technique in patients undergoing hysterectomy were strong enough to be compared with total laparoscopic hysterectomy [4]. However, there is still limited information about the feasibility, intraoperative complication, postoperative pain scores, and duration of surgery of the VaNOTES procedure in gynecologic practice.

This study evaluated whether the gynecological VaNOTES procedure contributes to an improvement in intraoperative hemodynamic data, postoperative pain scores, operation time, and hospital stay.

Materials and methods

Bakirkoy Dr. Sadi Konuk Training and Research Hospital Ethics committee approved (approval date: 20/05/2019-approval number:2019/237) the protocol of this study, which was conducted per the declaration of Helsinki. Assuming an alpha of 0.05, a power of 0.80, and a minimum 20% difference in terms of outcomes, the required sample size was at least 50 patients in each group. The charts of 110 patients who underwent hysterectomy and/or bilateral salpingo-oophorectomy (BSO) under general anesthesia either with conventional laparoscopy or VaNOTES method in a training and research hospital between March 2018 and April 2019 were reviewed retrospectively. Consent was obtained from the patients who were operated on in our clinic for the use of their medical data for clinical research purposes. Patients with an ASA 1-3 risk group who underwent hysterectomy and/or BSO surgery, without contraindications for pneumoperitoneum or the Trendelenburg position, were included in this study.

To avoid any selection bias, patients with previous endometriosis surgery, history of tubo-ovarian abscess, suspicion of pelvic inflammatory disease (PID), and intrauterine pregnancy were excluded from the study.

The patients received intravenous (IV) midazolam (0.02 mg/kg) for premedication. Induction of anesthesia was carried out with IV propofol (2-3 mg/kg), fentanyl (1-2 µg/kg) and rocuronium bromide (0.6 mg/kg). Anesthesia was maintained with an IV remifentanil infusion (0.05-0.1µg/kg) and sevoflurane at 0.7-1 minimum alveolar concentration (MAC). For postoperative analgesia, 1 gram of paracetamol and 1 mg/kg tramadol hydrochloride were administered intravenously at the end of the operation and 2x20 mg tenoxicam were given during hospitalization in the ward. The data of the patients were obtained from the hospital's electronic medical records.

Demographic data, perioperative hemodynamic data, Visual Analogue Scale (VAS) scores, and analgesic consumption at the 1st, 6th, and 24th postoperative hours were collected. Postoperative pain scores were evaluated with a Likert-type VAS (scoring from 0 = no pain to 10 = worst pain ever) after the 1st, 6th, and 24th hours postoperatively.

Statistical analysis

The parameters were analyzed by SPSS for Windows version 23.0. The Kolmogorov Smirnov test and histogram were used to clarify whether the data were normally distributed. The continuous variables were non-normally distributed in each group; therefore, non-parametric tests were used. The continuous variables were expressed as mean (standard deviation) or median (interquartile range (IQR) 25-75), while the categorical variables were expressed as n (%). The difference between the continuous variables of the two groups was calculated by the Student's T-test or the Mann-Whitney-U test. The Chi-square test was used in the analysis of categorical parameters. The changes in the perioperative findings between groups were evaluated with the mixed model for repeated measurements. $P<0.05$ was considered statistically significant.

In the post-hoc analysis where the duration of hospitalization was used as the data in hysterectomy cases, an 86% power was calculated for 69 patients who were screened retrospectively.

Results

The study population consisted of 110 patients who underwent hysterectomy (n: 69) and/or BSO (n: 41) under general anesthesia either with CL or the VaNOTES methods. The demographic and clinical findings of both groups are shown in Table 1. In both groups of patients who underwent hysterectomy or BSO operation, the median duration of anesthesia, median operation time, and hospital stay were lower in the VaNOTES group compared to the CL group (Table 1). The distributions of ASA scores did not differ significantly between the two groups.

Table 1: Distribution of demographic and clinical findings in BSO and hysterectomy cases

Variables	BSO		*P*-value	Hysterectomy		*P*-value
	CL	VaNOTES		CL	VaNOTES	
Preoperative period						
Age, years	42.2(12.4)	41.1(10.8)	0.759	49.4(7.9)	51.9(9.2)	0.246
Weight, kg	70.5(8.0)	74(12.5)	0.296	79.1(11.5)	78.7(15)	0.900
BMI, kg/m^2	26.5(3.6)	28(5.8)	0.317	30.2(4.9)	30.3(6.5)	0.941
ASA score						
ASA 1	5(26.3)	10(45.5)	0.33	3(9.7)	7(18.4)	0.257
ASA 2	14(73.7)	12(54.5)		27(87.1)	27(71.1)	
ASA 3	-	-		1(3.2)	4(10.5)	
Hemoglobin, mg/dL	11.9(2.0)	11.4(1.7)	0.411	11.2(1.9)	12.0(1.5)	0.092
Perioperative period						
Anesthesia time, minutes	127(90-150)	50(40-60)	<0.001*	175(138-220)	104(64-127)	<0.001*
Operation time, minutes	110(74-125)	35(25-45)	<0.001*	150(120-200)	90(45-110)	<0.001*
Removed uterine weight, gr	-	-	-	400(0-780)	250(0-815)	0.133
Postoperative period						
Hemoglobin, mg/dL	10.8(1.5)	9.9(1.6)	0.067	10.2(1.4)	10.7(1.4)	0.153
Verbal pain score						
1st hours	5(4-6)	4(3-5)	0.136	5(4-6)	4(3-5)	0.002*
6th hours	6(4-7)	4(4-5)	0.024*	5(5-6)	4(4-6)	0.136
24th hours	3(2-3)	2(2-3)	0.021*	2(2-4)	2(2-3)	0.728
CRP, mg/L	11(5-45)	10(5-19)	0.511	15(6-36)	10.5(5-22)	0.216
Hospital stay time, hours	69(47-72)	47(44-65)	0.009*	67(51-80)	54.5(42-63)	0.001*

Numerical variables are shown as mean (standard deviation) or median (IQR 25-75). Categorical variables are shown as numbers (%). * $P<0.05$ shows statistical significance. CRP: C-Reactive Protein, VaNOTES: Vaginally Assisted Natural Orifice Transluminal Endoscopic Surgery, CL: Conventional Laparoscopy, BSO: Bilateral Salpingoopherectomy

In patients who underwent a BSO, the median VAS scores at the postoperative 1st hour did not differ significantly in the VaNotes group compared to the CL group, but the median VAS scores were lower at the 6th and 24th hours. In patients who underwent a hysterectomy, the median VAS scores at the postoperative 1st hour were significantly lower in the VaNotes group compared to the CL group but were similar at the 6th and 24th hours (Table 1).

There was no difference between the groups in terms of perioperative heart rate, SpO2, and MAP and there was no hemodynamic instability requiring inotropes or vasopressors (Table 2).

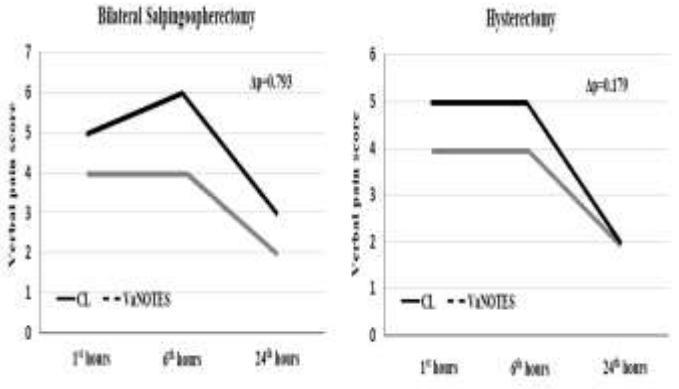
Table 2: Distribution of perioperative hemodynamic findings in BSO and hysterectomy cases

Variables	BSO		*P*-value	Hysterectomy		*P*-value
	CL	VaNOTES		CL	VaNOTES	
MAP, mmHg						
1 min	80.4(8.1)	81.8(10.9)	0.658	81.0(10.1)	82.6(8.9)	0.494
10 min	70.3(7.7)	73.6(6.7)	0.153	68.6(10.9	69.8(7.7)	0.621
20 min	69.5(7.8)	73.4(6.8)	0.097	71.5(7.7)	73.7(8.1)	0.263
30 min	73.9(9.7)	71.0(8.7)	0.319	69.4(9.0)	68.4(8.2)	0.662
40 min	78.3(9.8)	81.8(10.9)	0.295	73.7(7.5)	73.6(8.0)	0.934
50 min	73.3(7.1)	75.0(8.0)	0.458	68.4(5.9)	66.9(6.0)	0.332
60 min	69.5(8.0)	73.4(6.8)	0.100	71.5(7.7)	72.2(7.3)	0.728
*P*t	<0.001*	<0.001*		<0.001*	<0.001*	
Δ*P*	0.372			0.775		
Heart rate, beats/min						
1 min	85.1(16.8)	79.9(13.2)	0.280	82.2(16.0)	85.8(12.5)	0.288
10 min	72.8(12.4)	68.8(11.0)	0.272	70.8(12.9)	69.2(10.5)	0.568
20 min	70.6(11.1)	70.6(11.6)	0.997	70.4(10.0)	69.3(11.2)	0.681
30 min	68.7(11.3)	66.8(6.3)	0.101	70.1(9.7)	68.5(10.9)	0.533
40 min	65.4(8.7)	63.8(6.8)	0.345	63.1(7.5)	64.3(8.1)	0.520
50 min	63.3(7.0)	62.2(10.9)	0.108	71.3(11.0)	71.5(11.8)	0.932
60 min	69.1(9.8)	70.1(10.7)	0.739	71.3(11.0)	71.5(11.8)	0.932
*P*t	<0.001*	<0.001*		<0.001*	<0.001*	
Δ*P*	0.113			0.659		
SPO2						
1 min	100(100-100)	100(100-100)	0.999	100(100-100)	100(100-100)	0.999
10 min	100(100-100)	100(100-100)	0.999	100(100-100)	100(100-100)	0.999
20 min	100(100-100)	100(100-100)	0.999	100(100-100)	100(100-100)	0.999
30 min	100(100-100)	100(100-100)	0.999	100(100-100)	100(100-100)	0.999
40 min	100(100-100)	100(100-100)	0.999	99(99-100)	99(99-100)	0.999
50 min	100(100-100)	100(100-100)	0.999	99(99-100)	99(99-100)	0.999
60 min	100(100-100)	100(100-100)	0.999	99(99-100)	99(99-100)	0.999
*P*t	0.999	0.999		0.999	0.999	
Δ*P*	0.999			0.999		

Numerical variables with normal distribution are shown as mean (standard deviation) or median (IQR 25-75). * $P<0.05$ shows statistical significance. *P*t: Statistical difference of changes in laboratory findings in the group, Δ*P*: Statistical difference of changes in laboratory findings between groups, VaNOTES: Vaginally Assisted Natural Orifice Transluminal Endoscopic Surgery, CL: Conventional Laparoscopy, BSO: Bilateral Salpingoopherectomy

In patients who underwent BSO and hysterectomy, the postoperative changes in VAS scores were similar between the VaNotes and CL groups (Δ*P*=0.793, and Δ*P*=0.179, respectively) (Figure 1).

Figure 1: Changes in VAS scores



Δp: Statistical difference of changes in laboratory findings between groups, VaNOTES: Vaginally Assisted Natural Orifice Transluminal Endoscopic Surgery, CL: Conventional Laparoscopy, BSO: Bilateral Salpingoopherectomy

Nausea and vomiting due to opioid use in the postoperative period, pulmonary or mortal complications, or mortality were not observed among the two patient groups who underwent BSO, while the hysterectomy group was free of postoperative complications and mortality only.

Discussion

Since VaNOTES is a new surgical technique, data on anesthesia and postoperative pain management are limited. Considering the limited data in VaNOTES studies, our study has several important results. First, we found that the VaNOTES technique provides shorter anesthesia and operation time in hysterectomy compared to traditional laparoscopy. Second, VAS scores were low in the postoperative period in both the BSO and hysterectomy groups. Finally, VaNOTES was associated with early discharge in both patient groups. The VaNOTES technique suggests that the "Enhanced Recovery After Surgery (ERAS)" protocol is a suitable method, as it is less invasive and offers shorter anesthesia time, surgery time, and hospital stay compared to the traditional method.

In rare studies evaluating the feasibility of VaNOTES in hysterectomy procedures, the average uterine weight varies between 206-538 g, and it has been reported that NOTES reduces the duration of surgery, blood loss, and postoperative hospital stay [5-7]. Among these studies, the first randomized controlled study by Baekelandt et al. [5] presented and compared patients who underwent conventional total laparoscopic hysterectomy and VaNOTES hysterectomy. The uterine weight did not differ between the groups, and an approximately 1.5-fold reduction in operative time, total analgesic use, and hospital stay was reported with the VaNOTES procedure [5]. The largest hysterectomy series treated with VaNOTES in the literature was reported by Lee et al. In this study, the average operative time was 88 minutes, and the mean hospital stay was 2.8 days [6]. In the study of Kaya et al. [4] comparing the patients who underwent hysterectomy/BSO and adnexectomy with VaNOTES, the mean uterine weight, operation time, and hospital stay were 298 g, 85 minutes, and 2 days, respectively. To the best of our knowledge, our study is the second largest series in the literature, and similar findings were found in the VaNOTES protocol among hysterectomy patients. However, we determined that the VaNOTES technique is associated with a shorter operation time and hospital stay compared to CL. In addition, VaNOTES can reduce the length of hospital stay by providing significant advantages in wound infection and postoperative inflammatory response [8].

The ease of pneumovaginal tissue dissection and the surgeon's ability to enlarge the image with endoscopic imaging may play a role in the reduction of the operative time in the VaNOTES protocol. Difficulty accessing ligaments and uterine vessels in the large uterus and manipulation may prolong the operation time. An important advantage of VaNOTES in hysterectomy is the easy access to uterine vessels in the presence of a large uterus. It is difficult to close the feeding vessels in a limited area in the pelvis occupied by the large uterus with the laparoscopic approach [7]. We believe that the less manipulation requirement in VaNOTES eliminates this disadvantage and shortens the duration of surgery and anesthesia. The positive correlation we found between uterine weight and duration of anesthesia supports our idea. Wang et al. [9] compared the surgical results between VaNOTES hysterectomy and laparoscopic-assisted vaginal hysterectomy (LAVH). Operation time, amount of blood loss and postoperative hospital stay were lower in the VaNOTES group. They found more complications

in the LAVH group when uterine weight exceeded 500 grams. As a result, LAVH and VaNOTES groups were matched 1:1 with propensity score matching. Despite this matching, they found that there was a significant linear correlation between operative time and uterine weight in both groups, and similar results were obtained in terms of estimated blood loss. They concluded that VaNOTES can be safely performed on a large and prolonged uterus and that the operative efficiency of VaNOTES increases with the uterine weight [9]. On the other hand, in both case groups (BSO and hysterectomy), the duration of anesthesia was shorter in the VaNOTES technique. The short duration of anesthesia reduces the need for opioid and muscle relaxant use. Baekelandt et al. [5] also made a similar point.

VaNOTES procedures are reported to cause less pain [10, 11]. However, VAS scores may not differ compared to conventional methods [5]. In our study, the postoperative VAS values were significantly lower at the 6th and 24th hours in the BSO group who underwent VaNOTES and at the 1st hour in the hysterectomy group. However, VAS changes did not differ between the 1st-24th hours. Yang et al. [12] compared the patient who underwent VaNOTES hysterectomies and LAVH. In their study, demographic characteristics such as age, BMI, and uterine weights were similar in both groups. The VAS scores at the 12th and 24th hours did not differ between groups, but the operation time and hospital stay were lower in the VaNOTES group [12]. The change in VAS scores in our study is similar to that reported by Kaya et al [4]. Santos et al. [13] reported that only the closure of the vaginal cuff in VaNOTES caused this difference in VAS scores compared to the closure of 3-4 trocar accesses in the abdomen in conventional laparoscopy. The absence of transabdominal incision due to transvaginal access in the VaNOTES method reduces the need for postoperative analgesia by protecting the muscle groups in this area, which makes patients feel less parietal pain [1]. Visceral pain is more common in the VaNOTES technique. On the other hand, somatic pain is most prominent in conventional laparoscopic or open surgery techniques because of the skin incisions. Less postoperative pain leads to a reduction in postoperative narcotic analgesic use. This helps to avoid side effects such as nausea/vomiting, respiratory depression, constipation, and ileus and reduces hospital stay. In addition, it decreases wound infection rates and improves cosmesis [14]. The absence of an abdominal wall incision may prevent long-term wound healing and eliminate the risk of incisional hernia formation [15]. The innervation of the vaginal wall spreads to several spinal segments through the pelvic and hypogastric nerves (L2-S2). Therefore, regional anesthesia (spinal or epidural) techniques that provide sensory blockade on several spinal segments can be applied in VaNOTES surgery. Regional anesthesia may be preferred especially in patients with COPD and respiratory failure and the risk of postoperative respiratory complications may be reduced.

The main limitations of our study are its retrospective design and lack of randomization. Due to these limitations, the need or consumption of analgesic agents and opioid consumption could not be evaluated between the groups. Another limitation is that we could not reach patient data regarding perioperative intraabdominal pressure values and shoulder pain. Therefore, the effect of intra-abdominal pressures on perioperative respiratory and hemodynamic parameters, postoperative analgesic consumption, and possible shoulder pain could not be determined. Our results can only be generalized to the hospital where the study was conducted.

In our clinic, the preferred intra-abdominal pressure for VaNOTES cases is 10-12 mmHg, which is a lower pressure compared to the traditional method. The degree of the negative effect of CO_2 on the patient depends on both the intra-abdominal pressure and the exposure time. Even a difference of approximately 5 mmHg in intra-abdominal pressure can cause serious changes in respiratory physiology and mechanical ventilation strategies during the operation. Navarrove et al. [16] showed that the intra-abdominal pressure of the VaNOTES group in pigs was lower than that in the conventional group and reported its positive effects on hemodynamic and respiratory parameters. Low intraabdominal pressure may also reduce the incidence and severity of postoperative shoulder pain, which is common in laparoscopic surgery. Hua et al. [17] compared intraabdominal low and standard pressures for laparoscopic cholecystectomy. The incidence of shoulder pain and analgesic consumption were lower in the low-pressure group [17].

Conclusion

The use of the VaNOTES technique in gynecologic operations is less invasive, decreases surgical and anesthesia time, as well as pain intensity postoperatively, and improves the duration of the hospital stay. In the light of the obtained results, this new technique can provide clinical advantages for anesthesiologists as well as surgeons. Further prospective and randomized controlled studies are needed to evaluate VaNOTES in gynecologic surgery.

References

1. McGee MF, Rosen MJ, Marks J, Onders RP, Chak A, Faulx A, Chen VK, Ponsky J. A primer on natural orifice transluminal endoscopic surgery: building a new paradigm. Surg Innov. 2006 Jun;13(2):86-93. doi: 10.1177/1553350606290529.
2. Clark MP, Qayed ES, Kooby DA, Maithel SK, Willingham FF. Natural orifice translumenal endoscopic surgery in humans: a review. Minim Invasive Surg. 2012;2012:189296. doi: 10.1155/2012/189296.
3. Terzi H, Turkay U, Uzun ND, Salıcı M. Hysterectomy and salpingo-oophorectomy by transvaginal natural orifice transluminal endoscopic surgery (V-NOTES) assisted by an umbilical camera: Case report and new hybrid technique in gynecology. Int J Surg Case Rep. 2018;51:349-351. doi: 10.1016/j.ijscr.2018.08.053.
4. Kaya C, Alay I, Yildiz S, Cengiz H, Afandi X, Yasar L. The Feasibility of Natural Orifice Transluminal Endoscopic Surgery in Gynecology Practice: Single-Surgeon Experience. Gynecol Minim Invasive Ther. 2020 Apr 28;9(2):69-73. doi: 10.4103/GMIT.GMIT_84_19.
5. Baekelandt JF, De Mulder PA, Le Roy I, Mathieu C, Laenen A, Enzlin P, et al. Hysterectomy by transvaginal natural orifice transluminal endoscopic surgery versus laparoscopy as a day-care procedure: a randomised controlled trial. BJOG. 2019 Jan;126(1):105-113. doi: 10.1111/1471-0528.15504.
6. Lee CL, Wu KY, Su H, Wu PJ, Han CM, Yen CF. Hysterectomy by transvaginal natural orifice transluminal endoscopic surgery (NOTES): a series of 137 patients. J Minim Invasive Gynecol. 2014 Sep-Oct;21(5):818-24. doi: 10.1016/j.jmig.2014.03.011.
7. Su H, Yen CF, Wu KY, Han CM, Lee CL. Hysterectomy via transvaginal natural orifice transluminal endoscopic surgery (NOTES): feasibility of an innovative approach. Taiwan J Obstet Gynecol. 2012 Jun;51(2):217-21. doi: 10.1016/j.tjog.2012.04.009.
8. Fan JK, Tong DK, Ho DW, Luk J, Law WL, Law S. Systemic inflammatory response after natural orifice translumenal surgery: transvaginal cholecystectomy in a porcine model. JSLS. 2009 Jan-Mar;13(1):9-13.
9. Wang CJ, Huang HY, Huang CY, Su H. Hysterectomy via transvaginal natural orifice transluminal endoscopic surgery for nonprolapsed uteri. Surg Endosc. 2015 Jan;29(1):100-7. doi: 10.1007/s00464-014-3639-y.
10. Schaefer M. Natural orifice transluminal endoscopic surgery (NOTES): implications for anesthesia. F1000 Med Rep. 2009 Oct 29;1:80. doi: 10.3410/M1-80.
11. Robinson DR, Gebhart GF. Inside information: the unique features of visceral sensation. Mol Interv. 2008 Oct;8(5):242-53. doi: 10.1124/mi.8.5.9.
12. Yang YS, Kim SY, Hur MH, Oh KY. Natural orifice transluminal endoscopic surgery-assisted versus single-port laparoscopic-assisted vaginal hysterectomy: a case-matched study. J Minim Invasive Gynecol. 2014 Jul-Aug;21(4):624-31. doi: 10.1016/j.jmig.2014.01.005.
13. Santos BF, Teitelbaum EN, Arafat FO, Milad MP, Soper NJ, Hungness ES. Comparison of short-term outcomes between transvaginal hybrid NOTES cholecystectomy and laparoscopic cholecystectomy. Surg Endosc. 2012 Nov;26(11):3058-66. doi: 10.1007/s00464-012-2313-5.
14. Granberg CF, Gettman MT. Rationale for natural orifice transluminal endoscopic surgery and current limitations. BJU Int. 2010 Sep;106(6 Pt B):908-12. doi: 10.1111/j.1464-410X.2010.09668.x.
15. Hackethal A, Sucke J, Oehmke F, Münstedt K, Padberg W, Tinneberg HR. Establishing transvaginal NOTES for gynecological and surgical indications: benefits, limits, and patient experience. Endoscopy. 2010 Oct;42(10):875-8. doi: 10.1055/s-0030-1255756.

16.Navarro-Ripoll R, Martínez-Pallí G, Guarner-Argente C, Córdova H, Martínez-Zamora MA, Comas J, Rodríguez de Miguel C, Beltrán M, Rodríguez-D'Jesús A, Hernández-Cera C, Llach J, Balust J, Fernández-Esparrach G. On-demand endoscopic CO2 insufflation with feedback pressure regulation during natural orifice transluminal endoscopic surgery (NOTES) peritoneoscopy induces minimal hemodynamic and respiratory changes. Gastrointest Endosc. 2012 Aug;76(2):388-95. doi: 10.1016/j.gie.2011.10.015. PMID: 22817790.

17.Hua J, Gong J, Yao L, Zhou B, Song Z. Low-pressure versus standard-pressure pneumoperitoneum for laparoscopic cholecystectomy: a systematic review and meta-analysis. Am J Surg. 2014 Jul;208(1):143-50. doi: 10.1016/j.amjsurg.2013.09.027.

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Emergency care approach to sudden infant death syndrome

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Abstract

Sudden infant death syndrome, also called crib or cot death, is the sudden and unexpected death of an infant under one year of age who is thought to be completely healthy, and the cause of death cannot be explained by medical research. It is one of the important causes of mortality in childhood after the neonatal period in developed countries. The exact cause is unknown. The aim of our study is to present an emergency care approach by reviewing the recent studies on sudden infant death syndrome.

Keywords: Sudden infant death syndrome, Emergency care, Nursing

Introduction

Sudden infant death syndrome (SIDS) is defined as the sudden, inexplicable death of an infant under one year of age, even after a comprehensive case examination, including a full autopsy, medical and social history, and crime scene investigation [1]. This concept was first introduced in 1969 to draw attention to the sudden deaths of infants with similar clinical features [2].

Although there are different hypotheses, the inability to fully explain the etiopathogenesis poses a major problem. As in many countries, the question of whether SIDS or a suspicious death could not be answered in many cases in Turkey and these cases were evaluated in the category of "death with unexplained cause" [3].

Epidemiology

In 2016, approximately 3,600 sudden infant deaths (SID) occurred in the United States of America (USA). Cases occur among infants younger than one year of age with no apparent cause for the event [4]. Another study evaluating 94,038 infant deaths in Turkey between 2007 and 2012 reported that the incidence of SIDS increased by 2.1 times between 2007 and 2014, reaching 4% from 1.9% [5]. According to the 2016 death statistics of the Turkish Statistical Institute [6], babies who die between 1-4 months of age in Turkey constituted 22.6% of infant deaths; however, there is still no comprehensive study on the frequency of SIDS [7].

SIDS cases usually occur while asleep, during the first hours of the morning and at low ambient temperature. Seasonally, it most commonly occurs in the winter between October and April. The month in which infants are born is also related to the frequency of SIDS. While the frequency is the lowest in those born in early spring, it is the highest in those born in early August [8].

The fact that the frequency varies depending on ethnic groups and the higher occurrence in the children of mothers with blood groups (0) and (B), 10 times higher probability of its occurrence in consecutive siblings and 20 times in twins suggest that genetics may also have an etiological role [9].

Situations that cause a rapid and silent clinical picture during sleep have been defined as risks [10]. It has been thought that some chemical stimuli affect the upper respiratory tract or a disturbance in some metabolism or in the secretion of neurotransmitters cause sleep apnea, which, if prolonged, leads to death [9].

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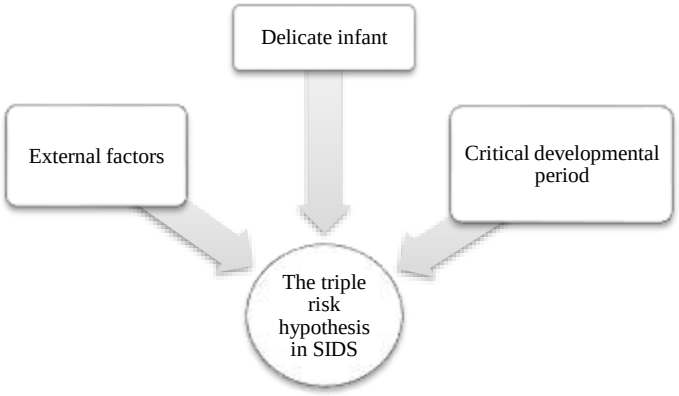
Risk factors

In the past centuries, scientists have put forward theories about the risk factors of SIDS. However, the most widely accepted hypothesis was suggested by Filliano and Kinney in 1994 [11] and includes the triple risk model (Figure 1).

Figure 1: The triple risk hypothesis in sudden infant death syndrome (SIDS)



Death occurs when infants with insufficient defense mechanisms and developmental disruptions are exposed to external stressors. SIDS is based on a triple risk model, which demonstrates that three factors that affect the infant occur simultaneously.

A triggering event such as apnea, hypoxia, insufficient cardiorespiratory control, cardiovascular pathologies, infections, anaphylaxis, preterm labor and lying prone, metabolic and congenital diseases, airway obstruction accompanying a brainstem anomaly or an anomaly in serotonin signaling play a role in the pathophysiology [12, 13].

In a study investigating the changeable and unchangeable maternal and labor-related risk factors associated with SIDS, it was determined that maternal smoking, chronic hypertension and gestational hypertension in the mother, premature labor, intrauterine growth retardation (IUGR) and being twins were prominent risk factors [14].

Many maternal, infant, and environmental risk factors were identified in the development of SIDS.

Maternal risk factors: The mother's low educational and socioeconomic status, single marital status, living alone, overweight, young age (especially 20 years old and below), previous miscarriage or the death of her previous children due to SIDS, consanguineous marriages, racial and ethnic origin are risk factors [15, 16]. Smoking status of mother, particularly during pregnancy, increases the risk of SIDS. Nicotine in the tobacco passes to the fetal circulation through the placenta and binds to the acetylcholine receptors in the fetal brain. In this process, it causes repetitive episodes of hypopnea, thereby bradycardia attacks, and changes the parasympathetic control of the heart, survival of cells and synapse formation. Nicotine also causes chronic hypoxia after labor due to decreased lung capacity of the fetus and increases the risk of respiratory tract infection by increasing the sensitivity of the infant [17, 18]. Since there is a risk of SIDS due to nicotine exposure, the use of electronic cigarettes during pregnancy should also be avoided [19]. An infant's exposure to cigarette smoke is an additional independent risk factor. Maternal use of harmful substances and alcohol are highly associated with SIDS in many studies [3].

Pregnancy-related risk factors: Pregnancy-related complications (placenta previa, ablatio placentae, premature rupture of membranes, increased alpha-fetoprotein level in the second trimester) infections, urinary infection, trauma experienced during pregnancy, malnutrition during pregnancy, frequent delivery, low maternal blood pressure in the third trimester of pregnancy, bleeding in the last trimester that causes anemia and inadequate prenatal care also increase the risk of SIDS [9, 15, 19]. Deaths are more common in infants whose mothers use barbiturate or narcotic drugs during pregnancy [20].

Risk factors regarding labor: Sedation or anesthesia during labor [9] and oxygenation with resuscitation performed during labor are in the risky group [15].

Infant-related risk factors: Premature infants, IUGR and infants with low birth weight are at great risk. In addition, it is more common in intrauterine passive smokers [21]. Studies have found that among infants with low birth weight, the rate of SIDS is 3-4 times higher than infants with normal weight. There is a 5-6-times increase in the risk of SIDS in infants with a history of SIDS in their siblings [22]. Cohort studies on twins have found the mortality rate twice as high as those of single infants [23]. The growth-development and nutritional status of the infant also pose a risk [24]. Among the risk factors, congenital or acquired diseases of the infant, including heart diseases (myocarditis, long Q-T syndrome, congenital heart disease), lung diseases (bronchiolitis, pneumonia), brain diseases (cerebral edema, subdural hemorrhage, meningitis encephalitis, intracranial hemorrhage) and blood diseases (sickle cell anemia) are of great importance [25]. Metabolic diseases constitute 5% of sudden and unexpected infant deaths. A family history of metabolic disease or sibling death with unknown cause, a clinical picture similar to sepsis before death, hyperventilation, feeding intolerance, vomiting, hypoglycemia, lactic acidosis, hyperammonemia suggest a metabolic disease. The most common metabolic disease that causes sudden unexpected infant death is fatty acid oxidation disorder. To exclude metabolic diseases, it is necessary to perform metabolic examinations for all infants with a risk of SIDS. However, since there may be a risk of recurrence in metabolic diseases or abuse, these conditions should be excluded before confirming the diagnosis [10].

Environmental factors: There is a strong relationship between the infant's lying position and SIDS and most deaths occur in the prone position [7]. Prone sleeping position is the strongest changeable risk factor for SIDS. In a case-control study, it was shown that the risk of SIDS increased 2.3-13.1 times in the prone sleeping position [26].

The National Institutes of Health (NIH) study suggested that the risk of aspiration was lower among patients in the supine position, since the trachea in infants lying on their back is on top. This proves that infants do not aspirate in case of vomiting during sleep and that lying on their back to breathe more comfortably is a factor that prevents SIDS [27]. In addition, despite the negative effects of the prolonged supine position on musculoskeletal and motor development, it has been reported that it is protective against sudden infant death syndrome due to the decrease in the arousal threshold and more frequent awakenings [28]. The US Food and Drug Administration (FDA)

warned that sleeping the infants on their side is associated with SIDS [29]. According to recent studies, U-shaped pillows have been shown to play a role in infant mortality [30].

Sleep environment: The use of a soft sleeping surface was found to increase the risk of SIDS in a case-control study. In another study, it was found that using a soft mattress in the prone position increased the risk 21 times [31]. The prone sleeping position increases the CO_2 level with re-breathing of expiratory air, particularly in infants who sleep in soft mattresses [32]. This position may also cause a reflexive displacement of the lower jawbone, obstruction of the pharynx, or closure of the nose, thereby an obstruction of the upper airway [33].

Couch or reclining chair, beads, polystyrene foam mattresses or mattresses with natural fiber, face cover, non-stretched bed sheet, blanket or quilt, pillows, toys and any other soft objects on the bed that cover the face while sleeping can increase the risk of SIDS by airway obstruction. Infants who are overdressed while asleep, swaddled tightly or sleep-in rooms that are overheated are also at higher risk. It has been recommended that car seats or strollers not be routinely used for sleeping [34, 35]. Otherwise, the risk of SIDS increases if infants do not have sufficient neck control to support their airways when they fall asleep. In addition, it should be kept in mind that aspiration due to increased gastroesophageal reflux (GER) may develop with the use of these equipment [36]. Although GER is physiological in the first months, recent studies have shown that lying in a supine position does not increase the risk of asphyxiation and aspiration in infants suffering from GER [37].

Again, an increase in the risk of SIDS has been observed in infants sharing the same bed with their parents [35, 38]. It has been shown in many studies that sleeping together and bed sharing increase the risk, particularly in infants younger than three months of age [26]. Parents being very tired, parental smoking, use of alcohol and sedative drugs and overweight increase the risk of SIDS among those who share their beds with the infant. A low birth weight of the infant, preterm labor and the infant being younger than 8-14 weeks are also risky conditions [39].

White noise

White noise is a continuous monotonous sound in the form of buzz that has a calming feature suppressing disturbing sounds in the environment [40, 41]. It is thought that while the infant is still in the womb, it is affected by the heartbeat of the mother and that re-finding this familiar sound and rhythm after birth has a relaxing effect on the infant [40, 42]. With the use of "sleep aids" (such as pacifiers, white noise, rocking cradles and swaddling), lonely and long-term infant sleep is targeted from an early age (deep sleep with minimal warnings). Inhibition of the stimulation response is a characteristic of vulnerable infants and increases with exposure to external stress [8]. Despite the potential benefits, white noise doesn't always offer risk-free peace and silence. In 2014, AAP tested 14 white noise devices designed for infants. They found that they all exceeded the recommended noise limits set at 50 decibels. In addition to increasing hearing problems, the study found the use of white noise to be risky in speech development. Based on the results of the AAP, pediatricians recommend placing any white noise device at least 2 m from the crib. In addition, it is recommended to lower the noise level of the device [43].

Typical characteristics of SIDS

In a well-developed infant, foamy blood around the nose, cyanosis in the lips and nail fold can be identified. Pulmonary edema is usually present and can be significant. Subacute inflammation in the upper respiratory tract, minimal stress effects on the thymus and adrenal glands and empty bladder have been found in most.

In infants died of SIDS, differences are found in the lung and other organs, brain stem and functions. SIDS mostly occurs in a healthy infant approximately 20 minutes after being put to sleep by his/her mother or his/her babysitter during the day or night. This was also associated with laryngospasm [8].

Diagnosis

All possible diseases and causes of death should be excluded for a diagnosis. For a complete investigation, standard protocols including detailed autopsy, scene investigation should be performed, and infant and family history should be obtained thoroughly [44].

In some cases, fatal child abuse can be confused with sudden infant death syndrome. In autopsy, it is difficult to differentiate between SIDS and incidental or intentional asphyxiation with a soft object [45]. Cases of infant deaths older than six months, simultaneous twin deaths, recurrent cyanosis, apnea, mouth and nose bleedings and unexplained sibling deaths may suggest abuse [7].

Especially in recurrent infant deaths, “Munchausen syndrome by proxy”, fatal child abuse and asphyxiation should be kept in mind. Intrathoracic petechial and intraalveolar hemorrhages seen in asphyxia deaths are also seen in SIDS cases [45].

Autopsy findings

The purpose of the autopsy protocol is to provide additional information to standardize autopsy practices, increase diagnostic accuracy and support the information obtained from clinical history and death events [2]. Autopsy is appropriate in cases of sudden and unexpected infant deaths, since all known causes cannot be excluded by history and imaging techniques [46].

The diagnostic criteria for SIDS:

- Term pregnancy,
- Normal clinical history, normal growth and development,
- Safe sleeping bed with inspection of the place of death,
- Other causes of death such as severe infections like sepsis, fluid-electrolyte imbalance, severe congenital anomalies, congenital metabolic diseases and poisoning should be excluded,
- Autopsy findings including cranium and cranial structures should support SIDS,
- There should be no macroscopic or microscopic findings suggestive of trauma, accident and/or serious disease,
- There should be no evidence of trauma on skeletal radiographs,
- There should be no evidence of intoxication with substances such as alcohol, medicine, etc.,
- There should be no findings suggestive of specific etiology in history and imaging,
- Based on the information obtained, the cause of death should be inexplicable [45].

External Examination

External examination begins by determining the infant's height and weight. In the meantime, changes specific to newborns such as vernix caseosa and lanugo covering the body are observed. In order to obtain information about the term of the child, it is necessary to carefully examine and photograph the head circumference, shoulder width, sole length, the length of the finger and toe nails, the umbilical cord and anogenital area [47]. The infant's body surfaces, oral and nasal cavities should be carefully examined, post-traumatic injuries or lesions on the skin, conjunctiva and mucosa should be checked and if any, petechiae should be recorded [2].

After the initial external examination is completed, a radiograph of the body should be taken to exclude bone injuries in the body. Infants who die of SIDS usually do not have external abnormalities. In other words, they give the impression of a well-groomed infant. Cyanosis on the lips and nasal wings and the presence of foamy, sometimes bloody mucus around the mouth and nose are among important findings. Dead examination findings are completely negative. There is no trauma [2].

Approach to SIDS in the Emergency Department

In deaths from SIDS, healthy infants are generally fed at night and put in their cribs. The next morning, the parents find their infant cold, purple and unresponsive. The emergency team is called and the infant is either transferred to the emergency room or stays at home depending on the emergency protocol. If the infant stays at his/her home and his/her room should not be touched until the forensic team reaches the scene [48]. Parents are asked questions to obtain information about the condition of the infant before death (health status, last feeding time, whether he/she was checked at night, sleeping position, his/her status when the infant was found dead) [49, 50].

If the infant is brought to the emergency room after he/she was found dead, the relevant units are called for a forensic medical examination. Scene investigation is important in determining the factors influencing the death of the infant. After the scene investigation is completed, the information gathered is reported to the physician who will perform the external examination and then the autopsy. In all cases, autopsy including detailed examination and toxicological examination are necessary to determine the cause of death [48, 49].

The parents may have difficulties accepting sudden death. Stress, anger and guilt are the most common reactions. Interviewing the family about death and waiting for autopsy results for a long time increases emotional stress [48]. All procedures should be explained and appropriate language should be used for interview techniques in traumatic cases. Healthcare professionals should explain to the family that it is routine to identify possible mechanisms leading to death. It should be specified that the questions in the interviews are asked to determine the risk factors and gather information and are not intended to accuse the family. Open-ended questions should be asked while taking history from the family in shock due to death and it should be emphasized that the collected information will be used by the forensic medicine team. It should be explained that autopsy performed to determine the mechanisms and etiology leading to sudden death is medically and legally necessary [50]. While allowing families to express their feelings, the necessary support and counseling should be provided to facilitate their coping with the trauma. They can be directed to group therapies, and informed that SIDS can be prevented to a great extent with the measures taken for preventable risk factors. Due to the lack of standard practice and a multidisciplinary approach, the number of studies in Turkey are very limited.

Conclusion

Emergency room personnel should be trained in the management of SIDS cases and develop appropriate approaches by working in coordination with the forensic team members. To reduce SIDS, the health personnel should be educated according to known etiologies, and parents should be informed as a preventive public health service. Families' awareness of the prevention of SIDS should be raised, standard procedures for case management and reporting should be developed and the family should be supported during the mourning process.

References

1. Center for Disease Control and Prevention: Sudden unexpected infant death and sudden infant death syndrome. 2016.
2. Yolaçan E, Bilge Y. Adli tıp açısından ani bebek ölüm sendromu: Derleme. Ankara Üniversitesi Tıp Fakültesi Mecmuası. 2020;73(1):1-4. doi: 10.4274/atfm.galenos.2020.47450.
3. Atılmıs ÜÜ, Dokgöz H, Yemisçigil A. Ani bebek ölüm sendromu. Adli Tıp Bülteni. 2006;11(1):30-9. doi: 10.17986/blm.2006111603.
4. Centers for Disease Control and Prevention: Sudden unexpected infant death and sudden infant death syndrome. 2018.
5. Dilli D, Köse MR, Gündüz RC, Özbas S, Tezel B, Okumus N. Recent declines in infant and neonatal mortality in Turkey from 2007 to 2012: Impact of improvements in health policies. Cent Eur J Public Health. 2016;24(1):52-7. doi: 10.21101/cejph.a4097.
6. T.C. Türkiye İstatistik Kurumu Başkanlığı. 2016.
7. Yıldız İ. Ani bebek ölüm sendromu ve adli hemşirelik yaklaşımı. Bull Leg Med. 2018;23:115-9. doi: 10.17986/blm.2018241706.
8. Aliustaoğlu İ. Doktorların ani bebek ölümü sendromu hakkındaki bilgi ve davranışlarına etki eden faktörler (Uzmanlık Tezi). Rize: Recep Tayyip Üniversitesi Tıp Fakültesi; 2018.
9. Korur Fincancı Ş, Kırangil B. Ani çocuk ölümleri sendromu. Turk J Path. 1988;4(2): 56-9.
10. Aliefendioğlu D, Güzoğlu N. Bir bebeğin aniden ölümü. Turk J Clin Lab. 2016;7(3):111-16.
11. Filiano JJ, Kinney HC. A perspective on neuropathologic findings in victims of the sudden infant death syndrome: the triple-risk model. Biol Neonate. 1994;65(3-4):194-7. doi: 10.1159/000244052.
12. Klaver EC, Versluijs GM, Wilders R. Cardiac ion channel mutations in the sudden infant death syndrome. Int J Cardiol. 2011;152(2):162-70. doi: 10.1016/j.ijcard.2010.12.051.
13. Canbal S. 0-1 yaş grubu bebeği olan annelerin ani bebek ölüm sendromu risk faktörleri (Uzmanlık Tezi). Gaziantep: Hasan Kalyoncu Üniversitesi; 2018.
14. Friedmann I, Dahdouh EM, Kugler P, Mimran G, Balayla J. Maternal and obstetrical predictors of sudden infant death syndrome (SIDS). J Matern Fetal Neonatal Med. 2017;30:2315-23. doi: 10.1080/14767058.2016.1247265.
15. Matthews T, McDonnell M, McGarvey C, Loftus G, O'Regan MA. Multivariate "time based" analysis of SIDS risk factors. Arch Dis Child. 2004;89(3):267-71. doi: 10.1136/adc.2002.025486.
16. Bubnaitiene V, Kalòdienò R, Kòvalas R. Case-control study of sudden infant death syndrome in Lithuania, 1997–2000. BMC Pediatrics. 2005;5:41-9. doi: 10.1186/1471-2431-5-41.
17. Sawnani H, Jackson T, Murphy T, Beckerman R, Simakajornboon N. The effect of maternal smoking on respiratory and arousal patterns in preterm infants during sleep. Am J Respir Crit Care Med. 2004;169(6):733-38. doi: 10.1164/rccm.200305-692OC.
18. Lavista Ferres JM, Anderson TM, Johnston R, Ramirez JM, Mitchell EA. Distinct populations of sudden unexpected infant death based on age. Pediatrics. 2020;145:e20191637. doi: 10.1542/peds.2019-1637.
19. Rajan R, Jarallah MA, Dashti R. E-cigarettes related health hazards-A 2020 Update. Int J Integr Cardiol. 2020;1:105. doi: 10.47275/2690-862X-105.
20. Getahun D, Amre D, Rhoads GG, Demissie K. Maternal and obstetric risk factors for sudden infant death syndrome in the United States. Obstet Gynecol. 2004;103(4):646-52. doi: 10.1097/01.AOG.0000117081.50852.04.
21. Perk Y. Ani bebek ölüm sendromu (SIDS). Eds. Ekşi A, Nobel Tıp Kitapevi, İstanbul, 2011, p: 14-23.
22. Ostfeld BM, Schwartz-Soicher O, Reichman NE. Prematurity and sudden unexpected infant deaths in the United States. Pediatrics. 2017,140(1). doi: 10.1542/peds.2016-3334.
23. Blair PS, Platt MW, Smith IJ, Fleming PJ. Sudden infant death syndrome and sleeping position in preterm and low birth weight infants: an opportunity for targeted intervention. Arch Dis Child. 2006;91(2):101-06. doi: 10.1136/adc.2004.070391.
24. Getahun D, Demissie K, Lu SE, Rhoads GG. Sudden infant death syndrome among twin births. J Perinatol. 2004;24:544-51 doi: 10.1038/sj.jp.7211140.
25. Erdoğan Ç. Denizli il merkezinde 0-12 ay arası bebeği olan annelerin ani bebek ölüm sendromu konusunda riskli davranışların belirlenmesi (Yüksek lisans tezi). Pamukkale: Pamukkale Üniversitesi; 2015.
26. Trachtenberg FL, Haas EA, Kinney HC, Stanley C, Krous HF. Risk factor changes for sudden infant death syndrome after initiation of Back-to-Sleep campaign. Pediatrics. 2012;129(4):630-8. doi: 10.1542/peds.2011-1419.
27. Moon RY. SIDS and other sleep-related infant deaths: Evidence base for 2016 updated recommendations for a safe infant sleeping environment. Pediatrics. 2016a;138(5). doi: 10.1542/peds.2016-2938.
28. National Institutes of Health (NIH). Eunice Kennedy Shriver National Institute of Child Health and Human Development/ Sudden Infant Death Syndrome (SIDS) and Other Sleep-Related Causes of Infant Death. 2014, 8.
29. Arpacı T, Altay N. Yenidoğan yoğun bakım ünitelerinde bireyselleştirilmiş gelişimsel bakım: Güncel yaklaşımlar. Turkiye Klinikleri J Nurs Sci. 2017;9(3):245-54. doi: 10.5336/nurses.2017-55289.
30. United States Food and Drug Administration Safety Alert: Sudden infant death syndrome. 2017.

31. Cottengim C, Parks SE, Erck Lambert AB, Dykstra HK, Shaw E, Johnston E, et.al. U-shaped pillows and sleep-related infant deaths, United States, 2004-2015. Matern Child Health J. 2020;24(2):222-28. doi: 10.1007/s10995-019-02847-9.
32. Rechtman LR, Colvin JD, Blair PS, Moon RY. Sofas and infant mortality. Pediatrics. 2014;134(5):e1293-300. doi:10.1542/peds.2014-1543.
33. Dales R, Burnett RT, Smith Doiron M, Stieb DM, Brook JR. Air pollution and sudden infant death syndrome. Pediatrics. 2004;113(6):628-31. doi: 10.1542/peds.113.6.e628.
34. Matturri L, Ottaviani G, Lavezzi AM. Sudden infant death triggered by dive reflex. J Clin Pathol. 2005;58(1):77-8. doi: 10.1136/jcp.2004.020867.
35. Moon RY. Air mattresses are not appropriate sleep spaces for infants. Am J Public Health. 2017;107(6):838-39. doi: 10.2105/AJPH.2017.303727.
36. Duncan JR, Byard RW. SIDS sudden infant and early childhood death the past, the present and the future. Adelaide (AU): University of Adelaide Press; 2018.
37. Moon RY. SIDS and other sleep-related infant deaths: Evidence base for 2016 updated recommendations for a safe infant sleeping environment. Pediatrics. 2016a;138.
38. Doering JJ, Salm Ward TC. The Interface among poverty, air mattress industry trends, policy and infant safety. Am J Public Health. 2017;107(6):945-49. doi: 10.2105/AJPH.2017.303709.
39. Academy of breastfeeding medicine clinical: Sleeping and breastfeeding. Revision, March. The Academy of Breastfeeding Medicine Protocol Committee. 2008.
40. Akça K. Beyaz gürültünün yenidoğanlarda emme başarısına etkisi (Yüksek Lisans Tezi). Erzurum: Atatürk Üniversitesi; 2014.
41. İlkaya NK. The effects of music, white noise, and ambient noise on sedation and anxiety in patients under spinal anesthesia during surgery. J Perianesth Nurs. 2014;29(5):418-26. doi: 10.1016/j.jopan.2014.05.008.
42. Jonsdottir V. Musical development in infancy the importance of early music stimulation. 2005.
43. Kristeen C. The pros and cons of using white noise to put babies to sleep. 2019.
44. Hauck FR, Thompson JMD, Tanabe KO, Moon RY, Vennermann MV. Breastfeeding and reduced risk of sudden infant death syndrome: a meta-analysis. Pediatrics. 2011;128(1):103-10. doi: 10.1542/peds.2010-3000.
45. Yukawa N, Carter N, Rutty G, Green MA. Intra-alveolar haemorrhage in sudden infant death syndrome: a cause for concern? J Clin Pathol. 1999;52(8):581–87. doi: 10.1136/jcp.52.8.581.
46. Gökçe S, Baysal SU. Ani bebek ölümü sendromu. İst. Tıp. Fak. Derg. 2004;67(1):56-61.
47. Acar K. Otopsi tekniği atlası. MN Medikal & Nobel; 2006.
48. Koehler SA. Sudden infant death syndrome deaths: The role of forensic nurses. J Forensic Nurs. 2008;4(3):141-42. doi: 10.1111/j.1939-3938.2008.00023.x.
49. Berkowitz C. Sudden infant death syndrome, sudden unexpected infant death and apparent life-threatening events. Advances in Pediatrics. 2012;59:183-208. doi: 10.1016/j.yapd.2012.04.011.
50. Celasin NŞ. Ani bebek ölümü sendromu. Ebeler için Yenidoğan Sağlığı ve Hastalıkları. Akademi Nobel Tıp Kitabevleri, Elazığ; 2016.

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Heterotaxy syndrome with accompanying azygos continuation of the inferior vena cava, patent ductus arteriosus and replaced common hepatic artery

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Informed Consent
The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Abnormal anatomical organization of thoraco-abdominal visceral organs and vascular structures is called "Heterotaxy Syndrome." Heterotaxy is generally classified under two main headings as polysplenia and asplenia syndromes. Complex cardiac anomalies are closely associated with poor prognosis in the patient group with asplenia syndrome. On the other hand, cardiac anomalies are less common in polysplenic syndrome. It is particularly important to define the findings accurately in the planning of surgical and interventional treatment. We present the findings of a patent ductus arteriosus (PDA) patient with co-existent heterotaxy syndrome associated with abdominal anomalies, such as polysplenia, azygos continuation of interrupted inferior vena cava, liver with midline localization, short pancreas, preduodenal portal vein, replaced common hepatic artery (HA) originating from the superior mesenteric artery (SMA) and left sided superior mesenteric vein to the SMA. To the best of our knowledge, there is no previous report of HA originating from the SMA found together with PDA and heterotaxy syndrome.

Keywords: Heterotaxy, Polysplenia, PDA, Replaced HA, SMA, IVC interruption

Introduction

Heterotaxy syndrome, also known as situs ambiguous, is a condition where the thoracoabdominal organs demonstrate abnormal arrangement across the left–right axis of the body [1]. Patients with heterotaxy syndrome have complex birth defects affecting the cardiac, respiratory, gastrointestinal, genitourinary and other systems [2]. The severity of heterotaxy syndrome varies depending on the specific abnormalities involved [1, 2]. High mortality rate is seen in patients with severe cardiac abnormalities while some patients have only mild health problems [1-3]. Radiological examinations are useful to accurately assess the abnormalities in patients with heterotaxy syndrome [4-7]. Herein, the CT findings of a 5-year-old patient who underwent radiological examination for suspicion of PDA and who was incidentally diagnosed with heterotaxy syndrome are presented.

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Case presentation

A five-year-old female patient was referred to the cardiology department of our hospital after recognizing a continuous murmur during cardiac auscultation in routine physical examination. In the echocardiographic examination, PDA was suspected. Contrast enhanced CT was performed for further evaluation. Late arterial images were obtained using a 64-slice CT scanner (Aqullion 64; Toshiba Medical System) with the following parameters: 80 kV tube voltage, 150-200 mA tube current, 1280.625 mm collimation, 0.67 mm section thickness, 1 mm increment, 0.2 mm/s table feed, 0.4 seconds rotation time. The patient was examined supine from suprasternal notch to the level of kidneys during free breathing, and a PDA with a diameter of 1.3 mm was detected (Figure 1 A-B). No anomaly was observed in the cardiac chambers and lung bronchi or lobes. The azygos vein was dilated in the posterior mediastinum and appeared to be the continuation of suprarenal IVC segment and drained into the superior vena cava (Interrupted IVC with azygos continuation) (Figure 2 A-B). The spleen was small in size with multiple adjacent accessory spleens (polysplenia) (Figure 3 A). The liver was located in the midline of abdomen and preduodenal portal vein (PDPV) was detected lying anterior to head of pancreas and duodenum (Figure 3 B). The pancreas was small in size. The common hepatic artery originated from the superior mesenteric artery (SMA) and the superior mesenteric vein (SMV) was observed on the left side of the SMA (Figure 4 A-B-C). In light of these findings, we diagnosed the patient with polysplenia syndrome. Written informed consent was obtained from the patient's father for the publication of this case report and tomography images.

Figure 1: Axial (A) and sagittal oblique (B) CT maximum intensity projection images. Patent ductus arteriosus, through which a slight passage of contrast material is observed (hollow arrow).

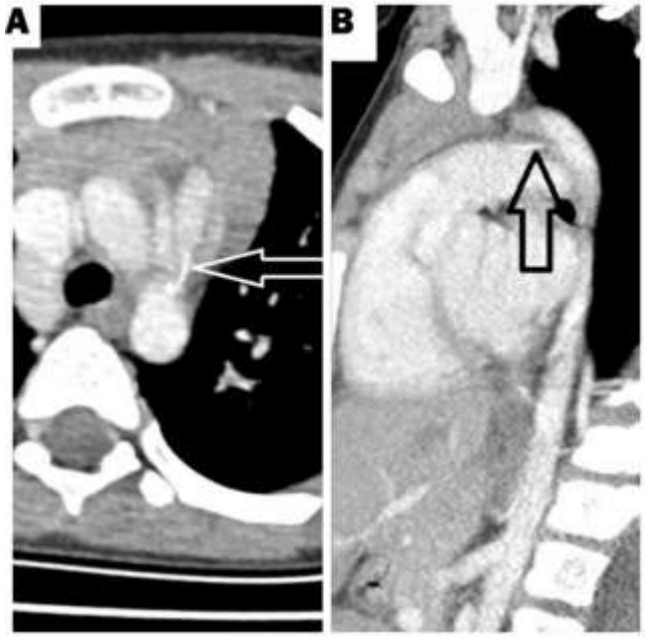


Figure 2: Sagittal reformat (A) and axial (B) CT images. Azygos continuation of interrupted inferior vena cava and opening superior to the vena cava.

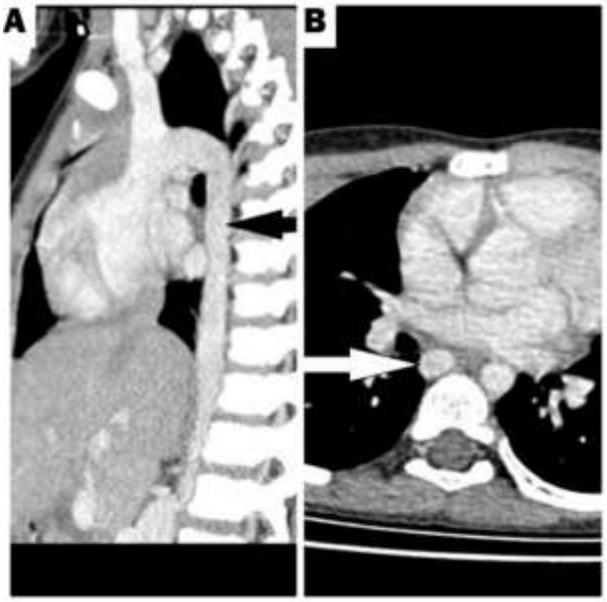


Figure 3: Axial CT images: A There are two nodular solid formations with similar density to the spleen indicating polysplenia. B. The falciform ligament and the liver is located in the midline (hollow arrow). Preduodenal portal vein is shown (solid arrow).

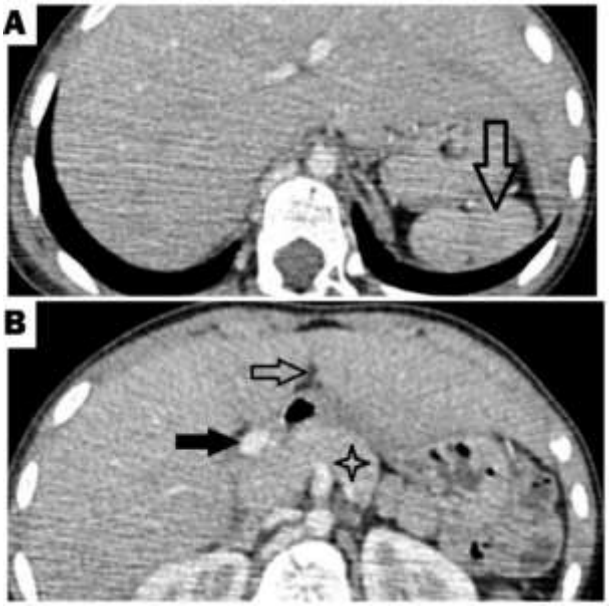
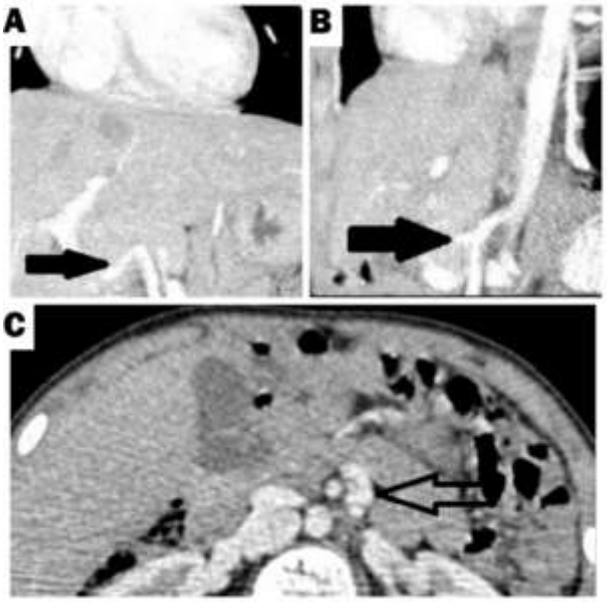


Figure 4: Coronal (A), sagittal (B) and axial (C) CT images. Hepatic artery arises from the superior mesenteric artery (solid arrow) and the superior mesenteric vein is located on the left side of superior mesenteric artery (hollow arrow).



Discussion

The exact cause of heterotaxy syndrome is unknown. It is thought to occur due to disruption of left-right axis determination in the early embryonic period. A single pathognomonic anomaly was not described for this rare entity. Recent studies have shown that more than 80 genes are required for normal asymmetric left-right organ development [3]. In general, there is a confusing classic method that classifies heterotaxy into two major syndromes, polysplenia (left isomerism) and asplenia (right isomerism) syndromes, where there are too many combinations of possible malformations, which is still a matter of debate today [1, 3, 8]. It is recommended to use the definition of "heterotaxy syndrome" instead and to describe associated findings afterwards [9]. However, this case will be discussed over the classical classification of heterotaxy syndrome. Our case had polysplenia without definite isomerism.

Polysplenia syndrome is a complex entity with a broad spectrum of abnormalities of thoracic and abdominal organs. The incidence of polysplenia syndrome is reported as 1 per 250,000 live births [3]. It is the condition in which there are multiple (2 to 16) spleens congenitally. There may be multiple spleens on the right or left side or in the midline, according to severity of the primary defect in lateralization. One of the other abdominal features in the polysplenia syndrome is a midline liver. This is a finding diagnosed in about half of patients with polysplenia [10]. In our case, the liver of the patient is located close to the midline. PDPV, stomach malposition, dorsal pancreatic agenesis, annular pancreas, short pancreas, duodenal atresia, biliary atresia, malrotation, and mobile cecum are among other abdominal findings diagnosed in cases with polysplenia [4, 9, 11-13]. In our case, while the stomach was located in the normal position, a short pancreas and PDPV were identified. Polysplenia syndrome with a variation of HA and the SMA is often diagnosed incidentally in patients by CT [14]. A limited number of articles were published in the literature, in which the HA originates from the SMA with heterotaxy syndrome, as in our case [3, 14-16]. In addition, the SMV was located on the left side of SMA, which is a suspicious finding in terms of intestinal malrotation. However, our patient had no abdominal complaints. Thus, a whole abdominal CT examination was not performed.

Polysplenia syndrome involves bilateral bilobed lungs, bilateral hyparterial bronchi and bilateral left atria in the thorax [1, 3]. Tracheobronchial structures, pulmonary vascularity and lungs segmental anatomy were normal in our patient. One of the common findings is azygos continuation of interrupted IVC [8]. As in our case, because of the developmental interruption of the suprarenal IVC segment, venous blood in the lower extremity flows into the superior vena cava (SVC) through azygos. Cardiovascular congenital anomalies such as atrial and ventricular septal defects, PDA, absent coronary sinus, abnormal location of the cardiac apex, common atrioventricular canal pulmonic stenosis, pulmonary atresia, an anomalous pulmonary venous connection, and an anomalous systemic venous return were reported in association with this syndrome [2, 17]. While no intracardiac pathology or main thoracic vascular anomalies were diagnosed in our case, the presence of PDA was confirmed. Peoples et al. [8] reported that 45 of the 127 autopsied cases of polysplenia had accompanying PDA. To the best of our knowledge, this is the first case report concerning the association between PDA, replaced common hepatic artery and heterotaxy syndrome.

Enhanced multislice CT is excellent radiological method for determining heterotaxy syndrome. Especially arterial and venous phase dynamic CT imaging series facilitate the identification of vascular and cardiac anomalies. Moreover, multiplanar and three-dimensional reconstructions can define congenital anomalies to an even greater advantage [4, 5, 7]. Technical factors can be adjusted to minimize the radiation dose to children. Ultrasonography may demonstrate abdominal anomalies such as midline localization liver, and multiple spleens. However, abnormally localized hollow organs can be mistakenly evaluated as masses [4]. MR imaging is an alternative method for detection of these anomalies [6]. Nevertheless, we did not perform additional MR imaging as our patient's family did not give their consent on the sedation process required for MR imaging of their 5-year-old child.

Heterotaxy syndromes with severe cardiac abnormalities are less frequent in adults because of the high mortality during early stages of life. In adult patients, heterotaxy syndrome is usually detected incidentally during radiologic examination or vascular interventions. It is important for surgeons or radiologists to detect and know these anomalies and anatomical characteristics before conducting surgical and interventional procedures [2, 14]. Thus, possible complications such as hemorrhage, vascular ligation, and organ injury may be prevented.

Conclusion

Heterotaxy syndromes encompass of a wide range of abnormalities affecting the thoracoabdominal organs and vascular structures. It has no characteristic radiological pattern, or typical laboratory findings. Since cardiovascular pathologies can have fatal complications, patients with a congenital heart disease (ASD, VSD, PDA, etc.) or those with an atypical position of the organs should be carefully examined in terms of other anomalies that make up the heterotaxy spectrum. Accurate diagnosis is also essential for proper planning of surgical and interventional procedures without the risk of vital organ injury.

References

1. Kim SJ. Heterotaxy syndrome. Korean Circ J. 2011 May;41(5):227-32.
2. Lagrotta G, Moises M. Heterotaxy Polysplenia Syndrome in Adulthood: Focused Review and a Case Report. Cureus. 2020 Jan 30;12(1):e6822.
3. Rameshbabu CS, Gupta KK, Qasim M, Gupta OP. Heterotaxy polysplenia syndrome in an adult with unique vascular anomalies: case report with review of literature. J Radiol Case Rep 2015;9(7):22.
4. Gayer G, Apter S, Jonas T, Amitai M, Zissin R, Sella T, et al. Polysplenia syndrome detected in adulthood: report of eight cases and review of the literature. Abdom Imaging. 1999 Mar-Apr;24(2):178-84.
5. Wolla CD, Hlavacek AM, Schoepf UJ, Bucher AM, Chowdhury S. Cardiovascular manifestations of heterotaxy and related situs abnormalities assessed with CT angiography. J Cardiovasc Comput Tomogr. 2013 Nov-Dec;7(6):408-16.
6. Murat SN, Yalcinkaya D, Yarlioglues M, Yigit H, Bozkurt U, Celik IE, et al. Diagnosis of Heterotaxy Syndrome in a Patient With Multiple Congenital Cardiac Malformations Using Magnetic Resonance Imaging. Circ Cardiovasc Imaging. 2020 Sep;13(9):e010307.
7. Kwon SH, Shin SY. Incidental adult polysplenia with situs inversus, interrupted inferior vena cava with azygos continuation, patent ductus arteriosus, and aortic branches variations: a case report. J Thorac Dis. 2018 Feb;10(2):E138-E141.
8. Peoples WM, Moller JH, Edwards JE. Polysplenia: a review of 146 cases. Pediatr Cardiol. 1983 Apr-Jun;4(2):129-37.
9. Applegate KE, Goske MJ, Pierce G, Murphy D. Situs revisited: imaging of the heterotaxy syndrome. Radiographics. 1999 Jul-Aug;19(4):837-52;discussion853-4.
10. Burton EC, Olson M, Rooper L. Defects in laterality with emphasis on heterotaxy syndromes with asplenia and polysplenia: an autopsy case series at a single institution. Pediatr Dev Pathol. 2014 Jul-Aug;17(4):250-64.
11. Fulcher AS, Turner MA. Abdominal manifestations of situs anomalies in adults. Radiographics. 2002 Nov-Dec;22(6):1439-56.
12. Tawfik AM, Batouty NM, Zaky MM, Eladalany MA, Elmokadem AH. Polysplenia syndrome: a review of the relationship with viscero-atrial situs and the spectrum of extra-cardiac anomalies. Surg Radiol Anat. 2013 Oct;35(8):647-53.
13. Emekli E, Gündoğdu E, Kebapçı M. Coincidence of left isomerism, malposition of cecum, dorsal pancreatic agenesis, and retroaortic left renal vein: A case report. J Surg Med. 2019; 3(11):812-814.

14. Liu J, Yang K, Wang J. Polysplenia syndrome with a rare variation between the common hepatic artery and the superior mesenteric artery in adults. Arch Med Sci. 2020 Aug 10;16(5):1263-1266.
15. Tsutsumi R, Nagata Y, Enjoji A, Ohno Y, Kamito H, Kanematsu T. Situs Ambiguous with Gastric Cancer: Report of a Case. Surgery Today, 2006;37:676-9.
16. De Wailly P, Metzler P, Sautot-Vial N, Olivier D, Meunier B, Faure JP. Pre-duodenal portal vein in polysplenia syndrome: clinical effects and surgical application. Surg Radiol Anat. 2011 Jul;33(5):451-4.
17. Celik M, Celik T, Iyisoy A, Guler A. An unusual combination of congenital anomalies in an adult patient: patent ductus arteriosus, Kommerell's diverticulum with aberrant right subclavian artery, and heterotaxy syndrome. Hellenic J Cardiol. 2011 Sep-Oct;52(5):469-72.

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Journal of Surgery and Medicine

The postoperative follow-up of varicose vein treatment with N-2-butyl cyanoacrylate application: A case series

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Abstract

N-2-butyl cyanoacrylate application to varicose veins is a novel minimally invasive method for varicose veins. The non-requirement for tumescent anesthesia is the most advantageous feature of this method. However, the intravascular persistence of the administered substance after the procedure has not been evaluated. In this study, the intravascular persistence of N-2-butyl cyanoacrylate was evaluated in the 6th month of administration. Three cases who underwent great saphenous vein ablation treatment with N-2-butyl cyanoacrylate were included in the study. The early postoperative and midterm (6th month) Doppler ultrasonography results were compared. The venous reflux in the sapheno-femoral junction (SFJ) level was totally treated after N-2-butyl cyanoacrylate administration in all patients. Ultrasonography revealed fully filled N-2-butyl cyanoacrylate at the treated levels of the saphenous veins. Similarly, 6th month's ultrasonography examinations revealed that N-2-butyl cyanoacrylate filled the great saphenous vein at the same level. It was observed that the rate of the vessel closed with N-2-butyl cyanoacrylate remained unchanged during six months. According to our results, intravenous N-2-butyl cyanoacrylate remains the same as at the time of administration without any degradation.

Keywords: N-2-butyl cyanoacrylate, Varicose vein, Treatment, Non-degradable

Introduction

Varicose veins disrupt the quality of life due to both cosmetic and physiologic complaints. Medical and surgical treatment are available. Especially the larger varicose veins with progressing venous reflux should be treated with open surgical or minimal invasive techniques. Endovenous laser, radiofrequency or chemical ablation methods can be selected for closure treatment of superficial venous reflux [1, 2]. Intravenous N-2-butyl cyanoacrylate application is one of the popular minimal invasive chemical ablation techniques for treating superficial venous reflux. The most advantageous features of this treatment are non-requirement of tumescent anesthesia and the ablation of varicose veins without high heat energy transfer to tissues [1-3]. However, its long-term intravascular behavior has not been adequately evaluated.

The current study aimed to investigate the midterm intravascular behaviour of N-2-butyl cyanoacrylate with venous Doppler ultrasonography.

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Informed Consent
The authors stated that the written consent was obtained from the patients presented with images in the study.

Conflict of Interest
No conflict of interest was declared by the authors.

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Case presentation

After preoperative venous ultrasonography, patients with great saphenous vein diameters higher than 5.5 cm (lower than 11 cm) and a greater than 3-second reflux duration (Figure 1) were selected for N-2-butyl cyanoacrylate ablation treatment. A 6F sheath was placed in the great saphenous vein just above knee under local anesthesia. Thereafter, N-2-Butyl cyanoacrylate was administered to just below the sapheno-femoral junction (SFJ) continuously via the commercially available application set (Musyan ™, Noegenix, Ankara, Turkey). Written informed consent was obtained from all patients.

Figure 1: A. Determination of saphenofemoral reflux by Doppler ultrasound B. Measurement of the saphenous diameter by Doppler ultrasound

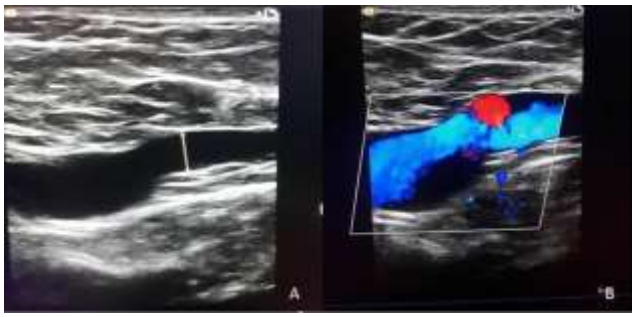


Figure 2: Evaluation of intravenous cyanoacrylate glue (Case 1: same level) by Doppler ultrasound A. Early postoperative period B. Sixth month

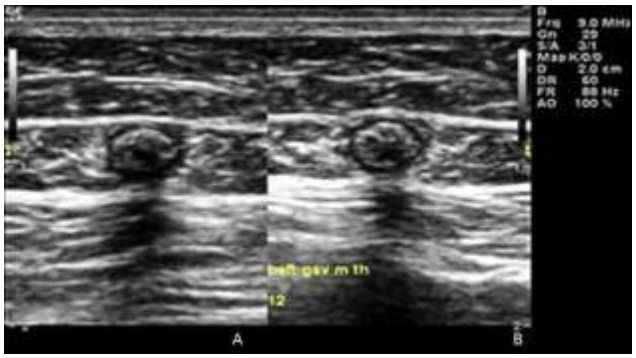


Figure 3: Evaluation of intravenous cyanoacrylate glue (Case 1: same level) by Doppler ultrasound A. Early postoperative period B. Sixth month

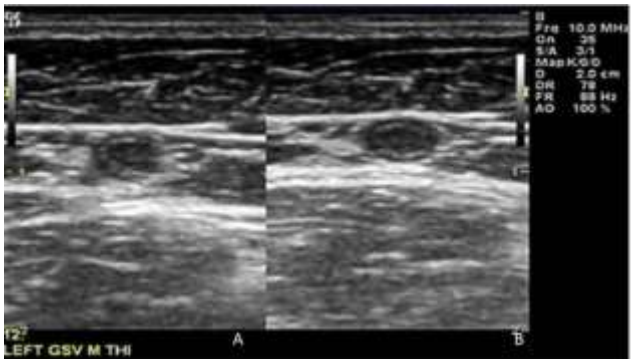
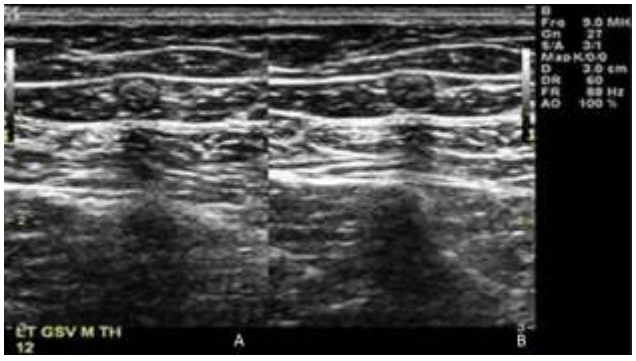


Figure 4: Evaluation of intravenous cyanoacrylate glue (Case 1: same level) by Doppler ultrasound A. Early postoperative period B. Sixth month



Case 1

A 54-year-old male patient visited the hospital with restless leg and edema complaints. Doppler ultrasonography revealed an 8.1 cm diameter of great saphenous vein with more than 5 seconds of venous reflux in the SFJ. The standard intravenous N-2-butyl cyanoacrylate ablation treatment was performed to the great saphenous vein under ultrasonography. The patient was discharged after the operation and the complaints of the patients dramatically regressed. Early postoperative ultrasonography and sixth month ultrasonography results were recorded for evaluating the venous reflux and the visualization of intravenous N-2-butyl cyanoacrylate. Total closure of the vein was observed with N-2-butyl cyanoacrylate at the sixth month without any degradation (Figure 2).

Case 2

A 60-year-old female patient was admitted to the cardiovascular surgery department due to enlarged superficial veins and complaints of poor cosmetic appearance. Doppler ultrasonography revealed a great saphenous vein, 9 cm in diameter, with more than 6 seconds of venous reflux in the SFJ. The standard intravenous N-2-butyl cyanoacrylate ablation treatment was performed to the great saphenous vein under ultrasonography. Additionally, a mini phlebectomy was performed to three varicose branches below the knee. The patient was discharged after the operation. Early postoperative ultrasonography and sixth month ultrasonography results were recorded for evaluating the venous reflux and the visualization of intravenous N-2-butyl cyanoacrylate. Total closure of the vein was observed with N-2-butyl cyanoacrylate at the sixth month without any degradation (Figure 3).

Case 3

A 47-year-old male patient working as a waiter was admitted to the cardiovascular surgery department due to swelling and cramping in the legs. Doppler ultrasonography revealed a great saphenous vein, 7.5 cm in diameter, with continuous venous reflux in the SFJ. The standard intravenous N-2-butyl cyanoacrylate ablation treatment was performed to the great saphenous vein under ultrasonography. The patient was discharged after the operation. His complaints resolved almost completely within a brief time. Early postoperative ultrasonography and sixth month ultrasonography results were recorded for evaluating the venous reflux and the visualization of intravenous N-2-butyl cyanoacrylate. Total closure of the vein was observed with N-2-butyl cyanoacrylate at the sixth month without any degradation (Figure 4).

Discussion

The lower extremity venous system consists of deep and superficial veins and perforating veins connecting them. The deep veins are the main drainage system of the lower extremities. These veins accompany the lower extremity arteries and are typically referred to by the same names as the arteries (common iliac vein, deep femoral vein, etc.) The superficial veins consist of the great saphenous vein (GSV), small saphenous vein (SSV) and the communicating veins that connect these veins. Unlike deep veins, superficial veins are not "indispensable" for the venous drainage of the leg [1-3]. However, venous insufficiency usually occurs over the superficial veins and appears as varicose

veins. Varicose veins are curved, large, palpable veins larger than 3 mm. In developed countries, its incidence tends to increase with age, and it is seen in 65% of women over the age of 45 years and 50% of men. Varicose veins may cause cosmetic problems such as pigmentation, lipodermatosclerosis, and functional limitations in the activities of patients, associated with pain. They may present with complications such as superficial thrombophlebitis (varicophlebitis), ulcerations and bleeding. Family history, advanced age, female gender, pregnancy, obesity, history of deep vein thrombosis, working in occupations that require standing for a long time are the dominant risk factors. Open surgical techniques or minimally invasive laser, radiofrequency or chemical ablation methods can be used in the treatment of varicose venous insufficiency [1-4].

The safe use of cyanoacrylates and the tissue compatibility of N-2-butyl cyanoacrylate, which is one of the long-chain cyanoacrylates, has brought the use of this adhesive material for intravenous treatment to the fore [5, 6]. This material was first documented for human use with N-2-butyl cyanoacrylate by Almeida et al. [4]. The two-year results of these practices were reported in 2015 [7]. The mean length of the vessel segment treated in this study, which included reports of 38 patients with clinical severities (according to CEAP classification) of C2-C4, saphenous diameters ranging from 3 to 12 mm (mean 6.7 mm), and reflux of more than 0.5 seconds, was 8 (9.1) cm. The mean procedure time was 21 minutes, quite short compared to Endovenous laser ablation (EVLA). Comparable to the EVLA method, 24-month closure rates were 92.2% [7]. Analysis of the venous clinical severity scores (VCSS) revealed that pain and edema decreased during follow-up and no paresthesia was observed. Adhesive or thrombus (clot) extension was observed in the SFJ, which resolved spontaneously within three months in the first eight cases (21.1%). It was suggested that administering the first injection 3-5 cm below the SFJ is no longer a problem. The absence of the need to use compression stockings after the procedure is another advantage. In this study, N-2-butyl cyanoacrylate was used as an adhesive [7]. Proebstle et al. [8] reported the results of the first prospective study of administration of N-2-butyl cyanoacrylate on 70 patients in the C2-C4 class with a saphenous diameter ranging from 3 to 10 mm (mean 7.8 mm) and a reflux of >0.5 seconds. In our cases, we observed total occlusion with N-2-butyl cyanoacrylate administration to varicose veins in the early and midterm follow-up period.

Previous studies indicated that the thermal degradation of low molecular cyanoacrylates, starting at the ends of polymer chains, is possible. However, these studies indicated that monomeric alkyl-α-cyanoacrylates can only be degradable at higher temperatures [9]. The other reports claimed that the longer-chain cyanoacrylate derivatives (R = C4H,, butyl) show weaker and slower degradation properties that result in safer metabolizing due to the reduced degradation products and decreased intense inflammatory response. It has been stated that this minimal degradation can take years. This is why the degradation products of these long-chain medical bonding materials are also difficult to detect in extraction studies. Because of this confidence interval, longer chain cyanoacrylate monomers are readily accepted by the FDA as medical adhesives [10, 11]. According to our results, intravenous N-2-butyl cyanoacrylate remained unchanged during the six-month follow-up.

Conclusions

N-2-butyl cyanoacrylate can treat venous reflux by providing total intravenous occlusion. Moreover, the ultrasonography images show that the N-2-butyl cyanoacrylate maintains venous full closure. This result can be interpreted in favor of considering the material as an implant. The long-term intravenous form of N-2-butyl cyanoacrylate should be evaluated to obtain more comprehensive results.

References

1. Lee AJ, Robertson LA, Boghossian SM, Allan PL, Ruckley CV, Fowkes FGR, et al.Progression of varicose veins and chronic venous insufficiency in the general population in the Edinburgh Vein Study. J Vasc Surg: Venous and Lym Dis. 2015;3:18-26.
2. Lim CS, Davies AH. Pathogenesis of primary varicose veins. Br J Surg. 2009;96(11):1231-42. doi: 10.1002/bjs.6798.
3. Tabatabaeifar S, Frost P, Andersen JH, Jensen LD, Thomsen JF, Svendsen SW. Varicose veins in the lower extremities in relation to occupational mechanical exposures: a longitudinal study. Occup Environ Med. 2015;72(5):330-7. doi: 10.1136/oemed-2014-102495.
4. Almeida JI, Javier JJ, Mackay E, Bautista C, Proebstle TM. First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. J Vasc Surg Venous Lymphat Disord. 2013;1:174-80.
5. Ronco V, Dard M. A novel suturing approach for tissue displacement within minimally invasive periodontal plastic surgery. Clin Case Rep. 2016;4(8):831–7.
6. Silverstein LH, Kurtzman GM. A review of dental suturing for optimal soft-tissue management. Compend Contin Educ Dent. 2005;26(3):163-6, 169-70
7. Almeida JI, Javier JJ, Mackay EG, Bautista C, Cher DJ, Proebstle TM. Two-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. Phlebology 2015;30:397-404.
8. Proebstle TM, Alm J, Dimitri S, Rasmussen L, Whiteley M, Lawson J, et al. The European multicenter cohort study on cyanoacrylate embolization of refluxing great saphenous veins. J Vasc Surg Venous Lymphat Disord 2015;3:2-7.
9. Carriles YR, Brito RA, Sánchez RM, Acevedo ES, Domínguez PR, Mueller WD. n-Butyl cyanoacrylate synthesis. A new quality step using microwaves. Molecules. 2014;19(5):6220-7. doi: 10.3390/molecules19056220.
10. Singh PK, Degala S, Shetty S, Rai VS, Das A. To Evaluate the Efficacy and Effectiveness of N-butyl-2-cyanoacrylate glue (TRU SEAL) in Closure of Oral and Maxillofacial Laceration and Surgical Incisions. J Maxillofac Oral Surg. 2019;18(1):131-8. doi: 10.1007/s12663-018-1111-6.
11. Petrie ME. Cyanoacrylate Adhesives in Surgical Applications: A Critical Review.2014;2(3):253-310.

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